

1,2-Oxazine *N*-Oxides as Catalyst Resting States in *Michael* Additions of Aldehydes to Nitro Olefins Organocatalyzed by α,α -Diphenylprolinol Trimethylsilyl Ether

Preliminary Communication

by **Dieter Seebach***, **Xiaoyu Sun**¹⁾, **Christof Sparr**¹⁾, **Marc-Olivier Ebert**, **W. Bernd Schweizer**, and **Albert K. Beck**

Laboratorium für Organische Chemie, Departement für Chemie und Angewandte Biowissenschaften,
ETH-Zürich, Hönggerberg HCI, Wolfgang-Pauli-Strasse 10, CH-8093 Zürich
(phone: +41-44-632-2990; fax: +41-44-632-1144, e-mail: seebach@org.chem.ethz.ch)

Dedicated to the memory of *Robert I. Ireland*, a dear friend and pioneering organic chemist

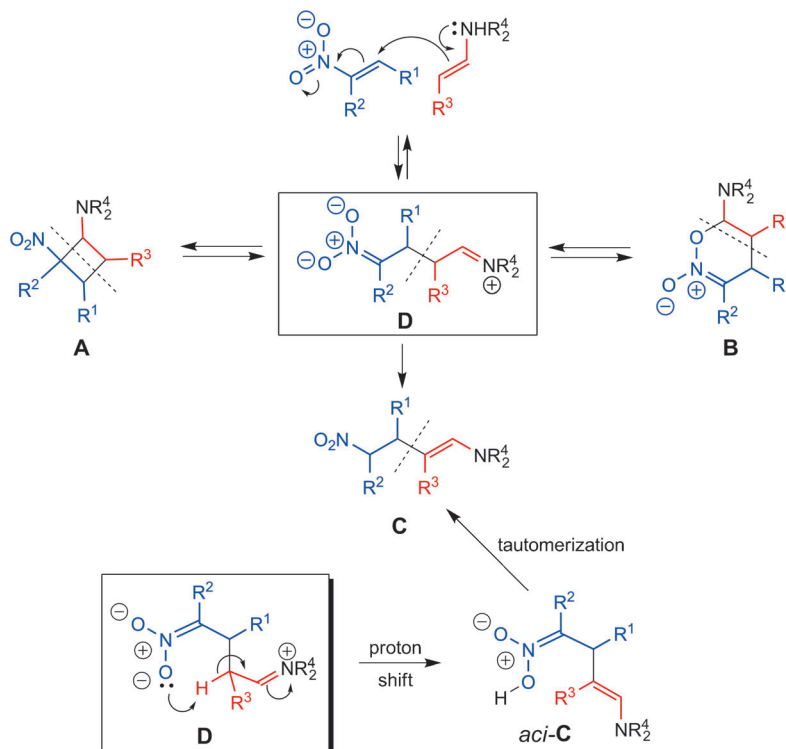
By combining enamines, derived from aldehydes and diphenylprolinol trimethylsilyl ether (the *Hayashi* catalyst), with nitroethenes ((D₆)benzene, 4-Å molecular sieves, room temperature) intermediates of the corresponding catalytic *Michael*-addition cycles were formed and characterized (IR, NMR, X-ray analysis; *Schemes 3–6* and *Fig. 1–3*). Besides cyclobutanes **2**, 1,2-oxazine *N*-oxide derivatives **3–6** and **8** have been identified for the first time, some of which are very stable compounds. It may not be a lack of reactivity (between the intermediate enamines and nitro olefins) that leads to failure of the catalytic reactions (*Schemes 3–5*) but the high stability of catalyst resting states. The central role zwitterions play in these processes is discussed (*Schemes 1* and *2*).

In stoichiometric reactions of aldehyde- and ketone-derived enamines with nitro olefins under anhydrous conditions, three types of products have been isolated, as long ago as 48 years: amino-nitro-cyclobutanes **A** (formally [2 + 2] cycloadducts), 1,2-oxazine *N*-oxides **B** (formally [4 + 2] cycloadducts), and ‘product enamines’ **C** [1]. The common intermediate precursor of these products is assumed to be a zwitterion **D** that is formed reversibly, and that may collapse, likewise reversibly, to the four- and six-membered ring, or else, undergo a proton shift, as shown in *Scheme 1* for an enamine derived from an aldehyde and a disubstituted nitroethene [1]. In principle, not only the collapse to a cyclic compound but also the proton shift could occur *intramolecularly* within the zwitterion, as indicated in the bottom part of *Scheme 1* (*cf.* the proposal made in [1c]). As with other ‘polar’ cycloadditions, the evidence for the involvement of an intermediary zwitterion is the non-stereospecific formation of the same diastereoisomeric product (mixture), no matter whether starting materials of (*E*)- or (*Z*)-configuration are employed [2]²⁾. This was shown for the *Michael* addition of diastereoisomerically pure (*E*)- and (*Z*)-morpholinoenamines to uniform (*E*)- or (*Z*)-nitro olefins [1m].

¹⁾ Postdoctoral co-workers 2011/2012.

²⁾ For this to be the case, the zwitterion involved may have a very short life-time; rotations around single bonds occur in the order of 10^{–11} s.

Scheme 1. Formation of Cyclobutanes **A**, 1,2-Oxazin N-oxides **B**, and Product Enamines **C** from Enamines and Nitro Olefins under Anhydrous Conditions. The zwitterion **D** plays a central role in its equilibration with the reactants, and the products **A** and **B**. The formation of the product enamine **C** could possibly occur intramolecularly, see **D** $\rightarrow$ *aci*-**C** $\rightarrow$ **C**.

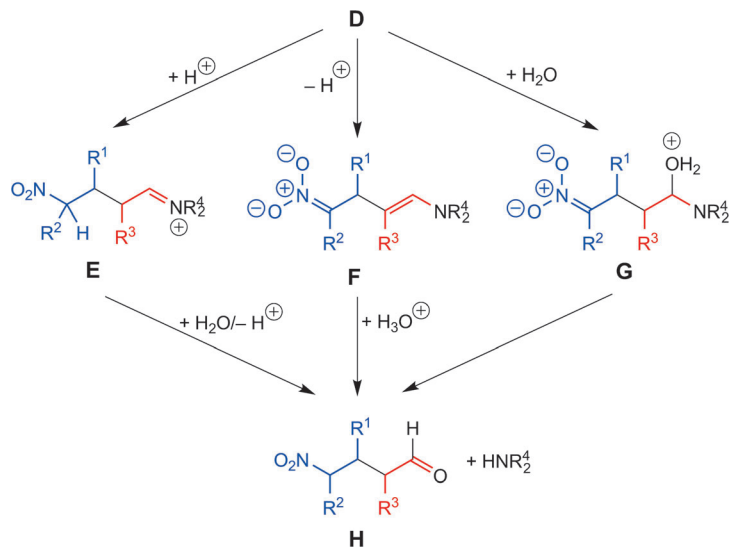


Acidic hydrolysis of all three types of (isolable) products **A**, **B**, and **C** has been shown to lead to γ -nitro aldehydes **H**³⁾, which, for the cyclobutane **A** and the heterocycle **B**, is assumed to, again, occur through the zwitterion intermediate **D**, by protonation ($\rightarrow$ **E**) and deprotonation ($\rightarrow$ **F**), respectively [1]; to draw the zwitterion out of its equilibria with the reactants and the cyclic compounds, a hydration of the iminium moiety ($\rightarrow$ **G**) may also be considered (Scheme 2)⁴⁾. In the mechanistic picture, as outlined in Schemes 1 and 2 the zwitterion plays the central role; the

³⁾ The statements made herein about aldehyde-derived enamines are *cum grano salis* also applicable to ketone-derived enamines.

⁴⁾ Although the relative and absolute configurations of the product γ -nitro aldehydes are not discussed herein, it is interesting to note that the configuration of the stereogenic center (bearing NO₂ and R²) results by a protonation step (*cf.* [3][4]) in all three routes from **D** to **H**, the configuration in the β -position to the aldehyde group (bearing R¹) is determined in the C,C-bond-forming step, again in all three routes, and the configuration in the α -position to the aldehyde group (bearing R³) is created in the C,C-bond-forming step *en route* **D** $\rightarrow$ **E** $\rightarrow$ **H** and **D** $\rightarrow$ **G** $\rightarrow$ **H**, and by diastereoselective protonation *en route* **D** $\rightarrow$ **F** $\rightarrow$ **H**, and, of course, also when the product enamine **C** is hydrolyzed (**C** $\rightarrow$ **H**).

Scheme 2. Trapping the Zwitterion **D** (from an aldehyde-derived enamine and a nitro olefin) to Form γ -Nitroaldehydes **H** in the Presence of H_2O (and acid) through Intermediates **E–G**



product-forming *bimolecular* reactions **D** $\rightarrow$ **E**, **F**, **G** compete with the *unimolecular* dissociation (back to enamine and nitro olefin) and with the *intramolecular* conversions to the cyclic (**A**, **B**) and the open-chain (**C**) isomers of the short-lived zwitterion⁵⁾.

In *Michael* additions of aldehydes to nitro olefins catalyzed by diphenylprolinol trimethylsilyl ether (the *Hayashi* catalyst **1** [5]), α,β -disubstituted γ -nitro aldehydes are formed with exceptionally high stereoselectivities, but the rate of conversion drops dramatically with increasing size and number of substituents on the nitro olefin component and in the α -position of the aldehyde used⁶⁾: thus, propanal and 3-methylbutanal do not react with 3,3-dimethyl-1-nitrobut-1-ene under catalytic conditions; on the other hand, the preformed enamine shown in *Scheme 3* forms the cyclobutyl derivative **2** with this *t*Bu-substituted nitro olefin under anhydrous conditions, as we have already shown in our previous paper⁷⁾. We have now isolated **2** and obtained an X-ray crystal structure depicted in *Scheme 3*⁸⁾. Thus, in this case the failure of the catalytic reaction is not due to lack of reactivity between the

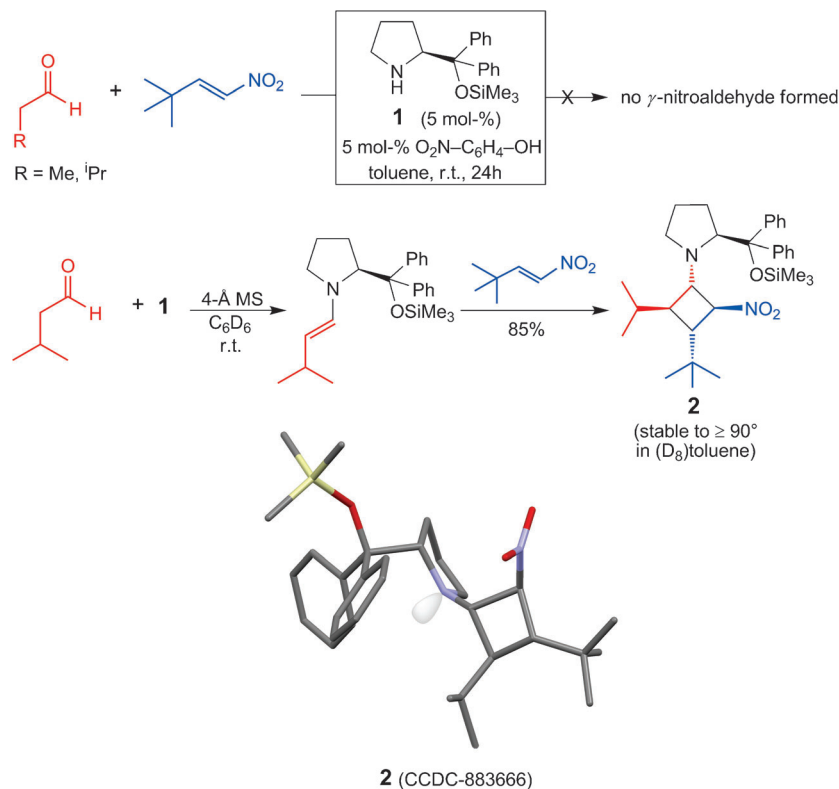
5) For the hydrolysis of the oxazine derivatives **B** under acidic conditions routes not involving the zwitterion have to be considered: a) protonation at an O-atom, followed by ring opening, would lead directly to the nitronic acid/iminium ion, the *aci*-nitro form of the nitro derivative **E**; b) a *Nef* reaction could eventually lead to a dialdehyde ($R^2 = H$) or an oxo aldehyde ($R^2 \neq H$).

6) This is surprising considering that the stoichiometric reactions of enamines with nitro olefins under aprotic conditions are exothermic ('react vigorously' [1a] and are often carried out below 0° [1b], or at -75° with slow warming [1m]), even with highly substituted reactants.

7) See Tables 3 and 4, and Fig. 3 in [1s].

8) The crystallographic data for compounds **2**, **3**, and **6** (*Schemes 3–5*) have been deposited with the Cambridge Crystallographic Data Centre (CCDC Nos. 883666–883668, resp.). These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

Scheme 3. Reaction between Aldehydes and '2-(tert-Butyl)-1-nitroethene' (= 3,3-dimethyl-1-nitrobut-1-ene) Does not Take Place under the Standard Conditions of Catalysis with the sec-Amine **1** [1s]; the 'Intermediate' (cf. Schemes 1 and 2) Cyclobutanes Are Too Stable and Become Catalyst Traps (MS = molecular sieves). Crystal structure of cyclobutane **2**⁸): orthorhombic space group $P2_12_12_1$, all-*trans* configuration; the virtual lone-pair lobe at the amino N-atom is *antiperiplanar* to the 'polar' C–C(NO₂) bond ($n_N \rightarrow \sigma_{CC}^*$ interaction), an arrangement, from which cyclobutane ring opening with formation of the corresponding zwitterion is expected to occur (cf. **B** in Scheme 3 of [1s]); *N* and *O* on the exocyclic bond of the pyrrolidine ring are *antiperiplanar*.



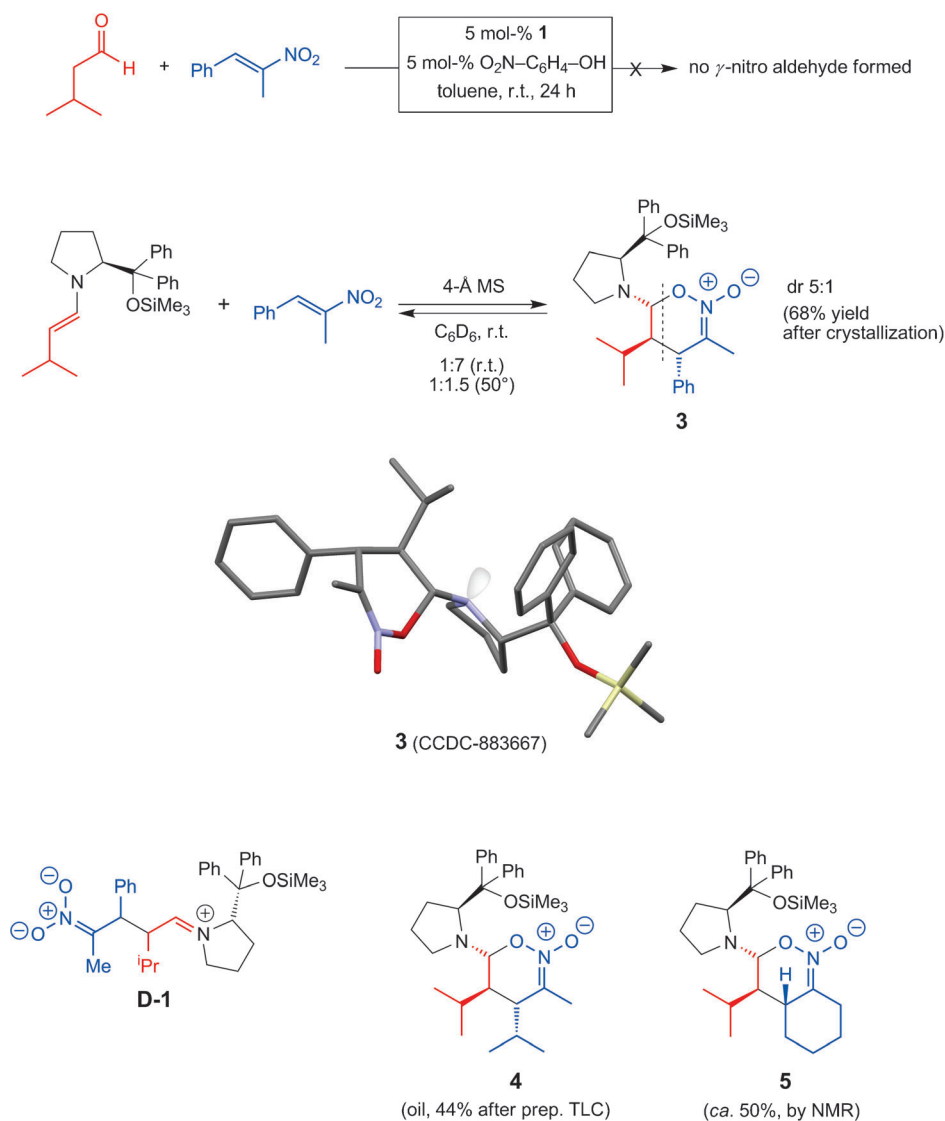
corresponding enamine and the nitro olefin, but it is rather caused by the fact that a cyclobutane is formed that is too stable to undergo ring opening back to the zwitterion, to be hydrolyzed according to Scheme 2, with the recovery of the amine catalyst. In the cyclobutane **2**, the catalyst 'rests forever' as a substituent.

In our search for reasons of lacking reactivity in *Michael* additions of aldehydes to nitro olefins with the Hayashi catalyst **1**, we have also studied (*E*)-2-nitro-1-phenylprop-1-ene, an α,β -disubstituted nitro olefin, which is assumed to show poor reactivity for steric reasons⁹), and we deliberately first chose the reaction with isovaleraldehyde (= 3-methylbutanal), providing an enamine intermediate with an ⁱPr group in β -

⁹) For a thorough discussion, entitled 'Adapting to Substrate Challenges: Peptides as Catalysts for Conjugated Addition Reactions of Aldehydes to α,β -Disubstituted Nitroolefins', with an extensive list of references, see [4].

position (*Scheme 4*). Indeed, there was no catalytic reaction under the standard conditions. When, however, a solution of the enamine in C_6D_6 (*cf.* *Scheme 3*) was

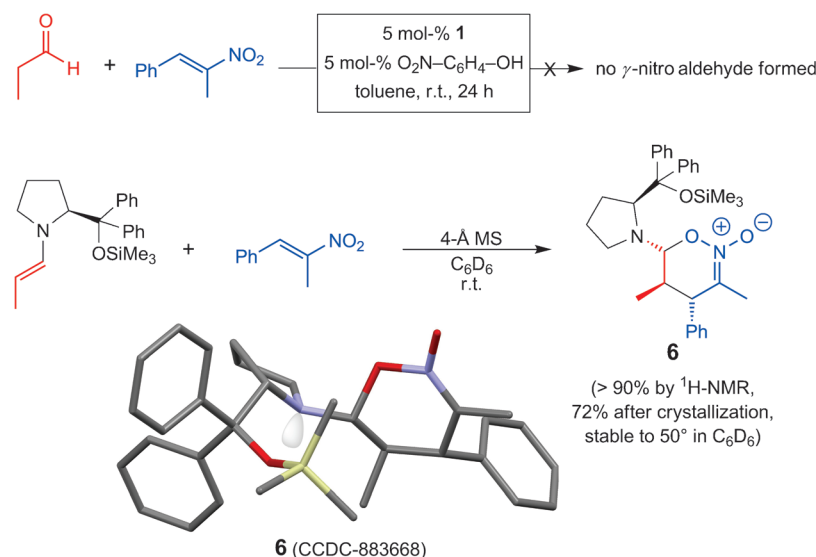
Scheme 4. Reactions of Isovaleraldehyde (=3-Methylbutanal) and Its 1-Derived Enamine with Disubstituted Nitro Olefins. There is no catalytic reaction with (*E*)-2-nitro-1-phenylprop-1-ene, but the enamine yields the 1,2-oxazine *N*-oxide **3** (see crystal structure with *ap*-conformation of the exocyclic bond on the pyrrolidine ring; monoclinic space group $P2_1$, only dominant conformation (75%) of the disordered Me_3Si group shown⁶). The 1,2-oxazine *N*-oxide **3** and the starting materials are in equilibrium (see the *T*-dependent ratio). Six-membered-ring heterocycles **4** and **5** have also been isolated or identified, respectively. The zwitterion **D-1**, which supposedly is involved in the formation and dissociation of **3**, is also shown.



treated with the nitro olefin in the presence of 4-Å molecular sieves, instantaneous formation of the 1,2-oxazine N-oxide **3** was evidenced by NMR analysis. A *temperature-dependent* heterocycle/starting materials ratio was established (by NMR integration of appropriate enamine and oxazine signals). The [4 + 2] cycloadduct **3** is very sensitive to moisture. Still, we were able to prepare single crystals for X-ray structure analysis (Scheme 4) of the major diastereoisomer. In view of the mechanistic scenario, as outlined in Schemes 1 and 2, we have to conclude that, in this case, the reaction of the corresponding zwitterion **D-1** (Scheme 4), with formation of products of type **E–G** (or with proton transfer to a nitro enamine **C**), is too slow under the catalytic conditions, *i.e.*, its collapse to the heterocycle **3**, and its dissociation back to enamine and nitro olefin are much faster. The oxazine derivative **4** (from (*E*)-4-methyl-2-nitropent-2-ene) was also isolated; it is stable enough to be purified by preparative TLC. Finally, 1-nitrocyclohexene gave the bicyclic nitronate **5** in a slow reaction; in this case, the analogous catalytic reaction has been shown to take place (20 mol-% **1**, 10 mol-% *m*-nitrobenzoic acid, 54 h, r.t., in CH₂Cl₂) [6]¹⁰.

We also looked at the reaction of the most simple aldehyde propanal and its Me-substituted enamine with the α,β -disubstituted nitro olefin (Scheme 5). The catalytic

Scheme 5. Reactions of Propanal and Its **1**-Derived Enamine with (*E*)-2-Nitro-1-phenylprop-1-ene, and Crystal Structure of the Product 1,2-Oxazine N-Oxide **6** (monoclinic space group *P*2₁)⁸). Unlike the situation in the structure of **3** (Scheme 4), in the crystal structure of **6** the exocyclic bond of the pyrrolidine has a *synclinal-exo* conformation. As in the structure of **3** (Scheme 4), the virtual lone-pair lobe on the pyrrolidine N-atom is *antiperiplanar* to the neighboring ‘polar’ C–O bond (see the N pyramidalization), establishing a stereoelectronic ($n_N \rightarrow \sigma_{C-O}^*$) stabilization; this is also the arrangement from which ring opening with formation of the corresponding zwitterion is expected to occur.

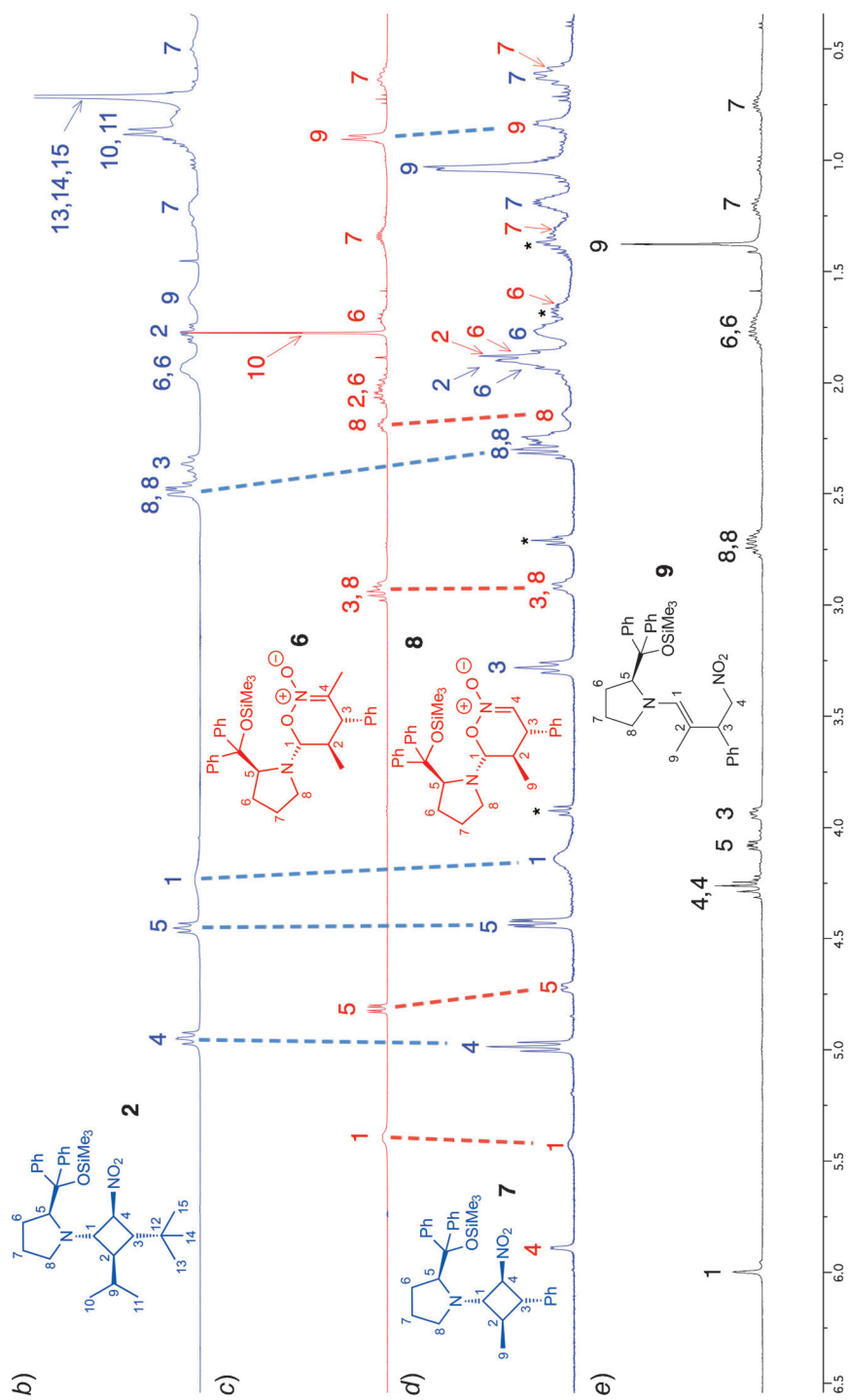


¹⁰⁾ Besides the crystal structure of **3** and **6**, and the NMR analyses, the characteristic nitronate ester IR band at *ca.* 1615 cm^{−1} of the products **3–6** is a further piece of evidence for their identity.

a)

¹ H-NMR (C ₆ D ₆ , ppm)					
	H ¹	H ²	H ³	H ⁵	
3	5.45	2.43	3.19	5.01	
4	5.09	2.09	1.50	4.95	
5	5.24	1.60	1.98	4.91	
6	5.40	2.00	2.92	4.82	
8	5.43	1.90	2.92	4.72	

Fig. 1. ¹H-NMR Data (a, b, and c) of the cyclobutane **2** and of the 1,2-oxazine N-oxides **3–6**, and comparison with the spectrum of the reaction mixture obtained by adding nitrostyrene to the **1**-derived enamine (C₆D₆, r.t.) (d), and with the spectrum of the 'final product' enamine (e; cf. Scheme 6). The atom numbering 1–8 in the formulae (cf. [1r]) is used for specifying the peaks from H-atoms in the spectra shown here and in Figs. 2 and 3. The signals marked with asterisk (*) stem from **1**. When comparing the data of compounds with and without a Ph group in the 4-position of the 1,2-oxazine N-oxide ring, shielding/deshielding effects are noticed. Note also that literature data [7] were obtained in CD₂Cl₂, while all our recordings were conducted in the aromatic solvents C₆D₆ or (D₈)toluene.



reaction again failed completely, but when the nitro olefin was added to a solution (in C_6D_6 over 4-Å molecular sieves) of the enamine in an NMR tube, the 1,2-oxazine *N*-oxide **6** had formed more or less quantitatively, before we arrived at the NMR spectrometer to record the spectrum. The oxazine derivative **6** with Me_2 and Ph substituents is *much* more stable than the Me-, Ph-, and iPr -substituted one, *i.e.*, **3** (*cf.* Scheme 4), and crystals suitable for X-ray analysis were readily obtained (see the structure in Scheme 5). When a solution of compound **6** in C_6D_6 (over 4-Å molecular sieves) was heated to 50° there was no sign of dissociation to enamine and nitro olefin, while **3**, with the more bulky iPr substituent, is in equilibrium with its precursors at room temperature (Scheme 4). Thus, the failure of the Hayashi catalyst **1** in the case shown in Scheme 5 is *not* caused by missing reactivity between the intermediate enamine and the nitro olefin but by the chemical property of the corresponding oxazine derivative **6**, which provides an irreversible trap for the amine catalyst, just like the cyclobutane **2** discussed above (*cf.* Schemes 2 and 5).

With the characteristic NMR data available for both, the cyclobutanes [1s] and the 1,2-oxazine *N*-oxides derived from aldehyde enamines and nitro olefins, we revisited the spectra obtained in our original work [1s] on cyclobutane formation in the *Michael* additions with catalyst **1**, to look for minor, hitherto not assigned peaks. Of particular interest was the combination of the simplest reactants, propanal and nitrostyrene, the prototype case also studied by Blackmond and co-workers [1q][1r]. When mixing the enamine and the nitro olefin in a 1:1 ratio (NMR tube, C_6D_6 , 4-Å molecular sieves, r.t.), the reactants disappeared immediately, and the signals from the cyclobutane **7** appeared, as assigned previously [1q][1s] (Fig. 1, c). Besides the cyclobutane (*cf.* Fig. 1, b), however, another compound was formed, giving rise to NMR signals matching, in shift and multiplicity, those of the oxazine derivatives' H^1 -, H^2 -, H^3 -, and H^5 -atoms (Fig. 1, a, c, and d); furthermore, a low-field signal (δ 5.9 ppm) was detected, which is characteristic for the H-atom next to the N-atom in 1,2-oxazine *N*-oxides that are unsubstituted at C(3) [7][8] (*i.e.*, H^4 in Fig. 1, d)¹¹⁾. Since some NMR peaks from the two compounds overlapped (see, *e.g.*, those of H^2 -atoms near 1.9 ppm), we recorded a 2D-COSY spectrum for safer peak assignment to overcome this problem. As is evident from Fig. 2, there are cross-peaks A, B, and C between H^1 and H^2 , H^2 and H^3 , and H^3 and H^4 , respectively, of the new species, as expected for the 1,2-oxazine *N*-oxide **8**. Thus, in this case a mixture (*ca.* 4:1) of the four- and of the six-membered rings, **7** and **8**, respectively, is formed (see Scheme 6). When the solution was kept at r.t. for 15 h, the cyclic compounds completely disappeared¹²⁾, and the product enamine **9** was formed quantitatively (10:1 mixture of diastereoisomers (NMR analysis); see Fig. 1, e, and bottom part of Scheme 6). To see, whether the four- and six-membered-ring compounds

¹¹⁾ In CD_2Cl_2 , the chemical-shift range of H–C(3) and C(3) in 1H - and ^{13}C -NMR spectra of 1,2-oxazine derivatives of this kind are 6.3–6.4 ppm and 113–117 ppm, respectively [7]; the ^{13}C signal of C(3) in **8** is observed at δ 112 ppm.

¹²⁾ The ratio **7/8** remained constant over this period of time. For one of several possible mechanisms of this conversion, see Scheme 1: **A**, **B** $\rightarrow$ **D** $\rightarrow$ *aci*-**C**. After mixing the enamine with nitrostyrene in K_2CO_3 -dried CD_2Cl_2 and immediately recording an NMR spectrum, we detected only signals corresponding to the product enamine **9** (no sign of starting material, or of four- or six-membered ring was detected in this solvent!). Note that successful catalytic additions of aldehydes to nitrocyclohexene by Gelman and co-workers were carried out in CH_2Cl_2 [6].

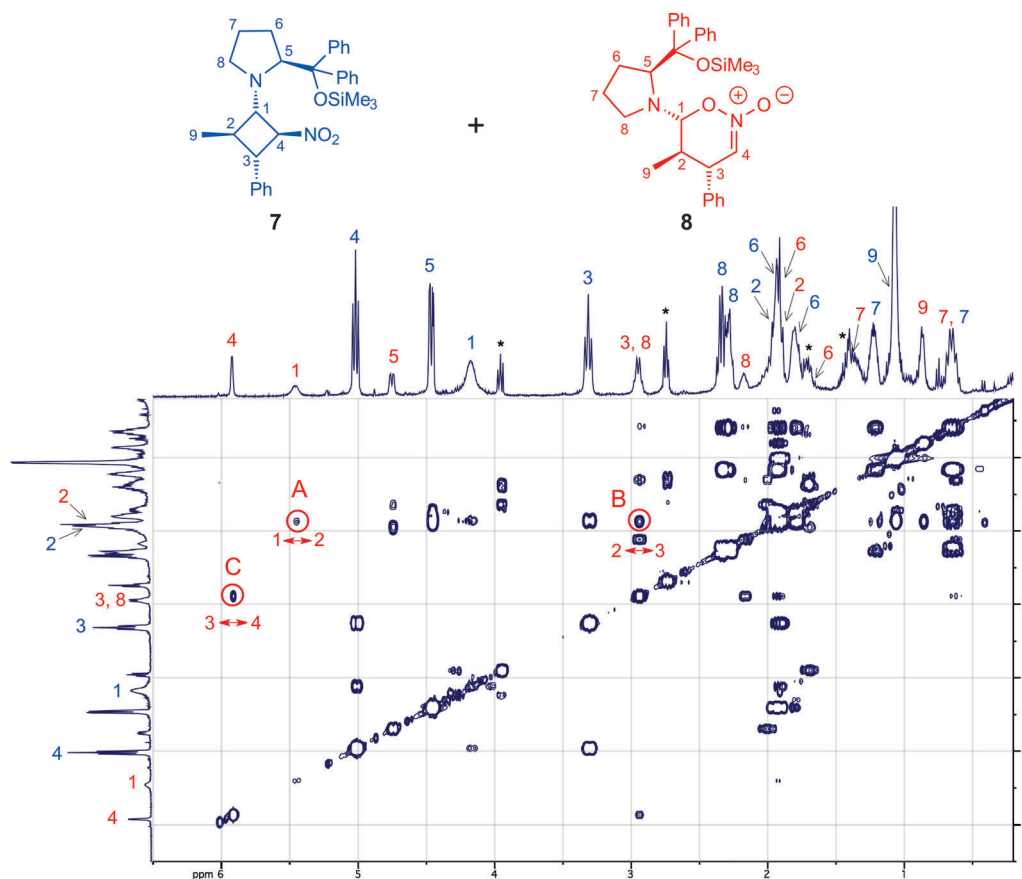


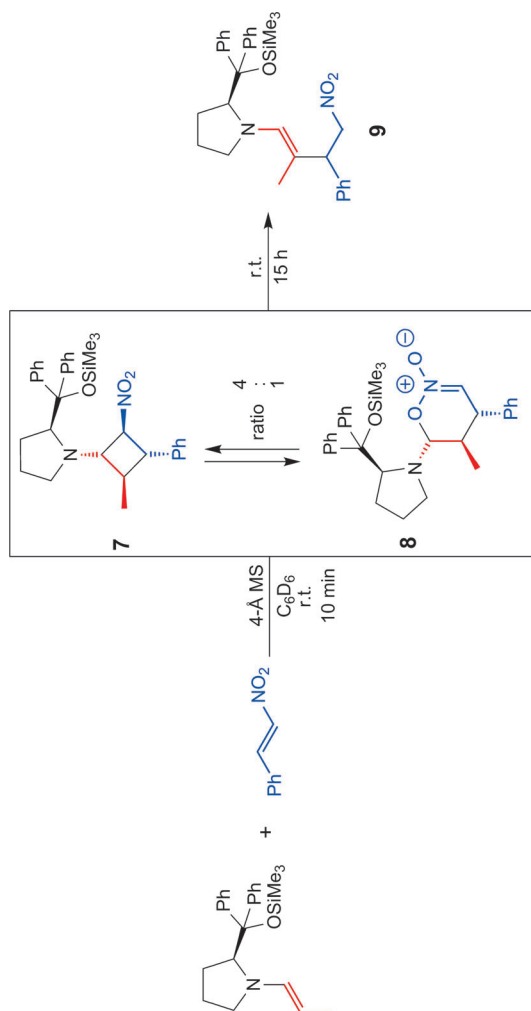
Fig. 2. Absolute-value COSY spectrum of the mixture of the [2+2] and the [4+2]cycloadducts **7** and **8**. Peak designation as in Fig. 1. The cross-peaks A, B, and C, marked in red, clearly show that there are four consecutive H-atoms, H¹, H², H³, and H⁴, in the six-membered ring just like in the cyclobutane. The spectrum was recorded immediately after mixing the enamine solution with nitrostyrene, and the recording was completed within 20 min.

equilibrate with each other, we also recorded an EXSY spectrum of a (D₆)benzene solution containing **7** and **8** (Fig. 3), which provided unambiguous evidence for exchange between these two species. In accordance with the general mechanistic picture outlined in Scheme 1, we would suggest that this equilibrium, as well as the conversion to the product enamine **9**, take place through the intermediate zwitterion of type **D**.

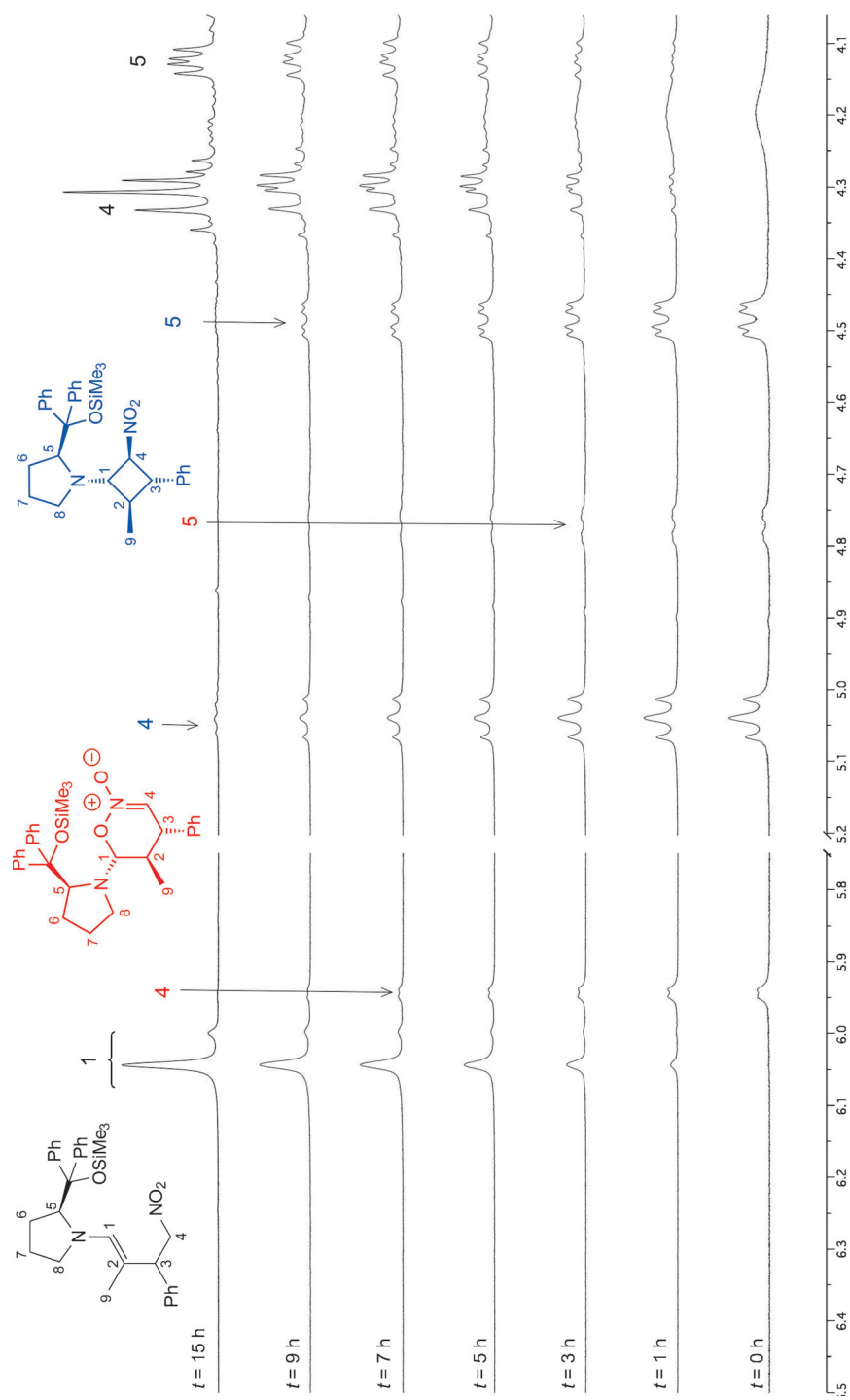
At this point, we have to refer to a recent paper by Blackmond and co-workers [1r], in which the compound identified as 1,2-oxazene *N*-oxide **8** by us was assigned¹³⁾ as being nitronate anion **10**, equilibrating with the cyclobutane **7** by protonation/deprotonation (Scheme 7). The authors realized that a direct, elimination-type cyclobutane ring opening, as depicted in **J**, is unfavorable and make the statement:

¹³⁾ ... using a 2D-NOSY spectrum, identical to that shown in Fig. 3 (proof of equilibration).

Scheme 6. *Formation of an Equilibrium Mixture of Cyclobutane 7 and the 1,2-Oxazine N-Oxide 8 (4:1) upon Mixing the Propanal-enamine with Nitrostyrene in C₆D₆.* Under the standard catalytic conditions, propanal and nitrostyrene react to the corresponding γ -nitro aldehyde [1q-s]. NMR Analysis of the equilibrium mixture **7/8** over 15 h shows that there is a complete conversion to the product enamine **9** under the conditions specified.



Scheme 6 (cont.)



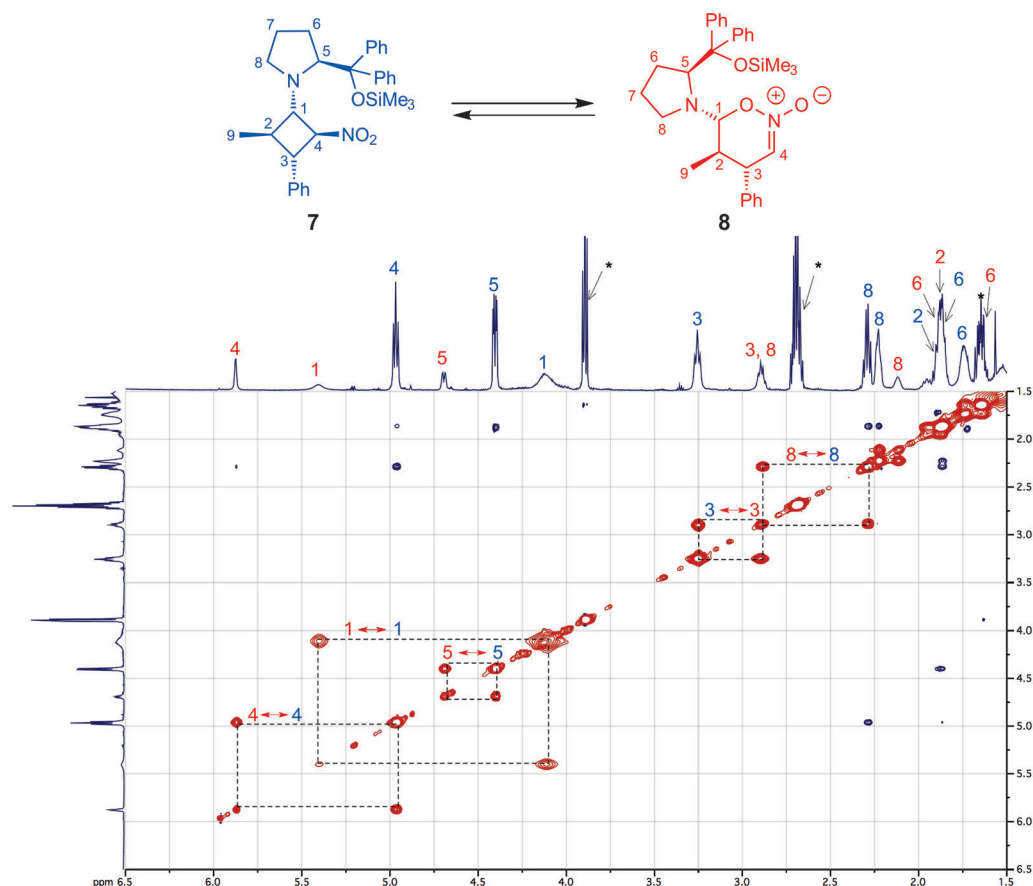
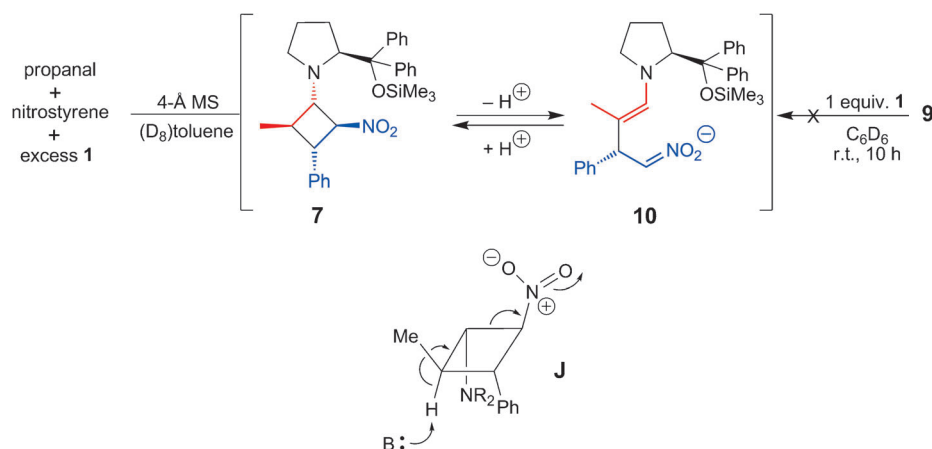


Fig. 3. EXSY Spectrum of the mixture **7/8** (C_6D_6 , r.t., mixing time 500 ms). Immediately after mixing the reactants, the spectrum was recorded which took 1 h to be completed. Peak numbering and colors refer to the H-atoms in positions as shown in the formulae, see also Figs. 1 and 2. For an identical spectrum, see [1r]. The spectrum establishes equilibration between **7** and **8**.

... ‘a step that may represent sequences of elementary reactions combined into one kinetically meaningful step’ ([1r] and Footnote 14 therein). Apart from the incorrect structural assignment, we consider this proposal unlikely from a purely intuitive chemical point of view, since it claims the occurrence and observation by NMR of a free nitronate anion under strictly anhydrous conditions in toluene solution (the counterion would have to be H-1^+)¹⁴, and it suggests an energetically uphill conversion of an open-chain enamino-nitronate to a cyclobutane upon protonation.

¹⁴) This acid H-1^+ is proposed to eventually protonate the nitronate anion moiety of **10** to produce – irreversibly – the product enamine **9** [1r]. On the other hand, this acid H-1^+ would also have to protonate the enamine moiety of **10** to generate the cyclobutane in the proposed equilibrium. With $\text{p}K_{\text{a}}^{\text{H}_2\text{O}}$ values of protonated pyrrolidine of 11.3, and of nitroethane of 8.6 (CH_2) and ca. 4.5 (*aci*-nitro form), pyrrolidine should actually deprotonate the nitro compound in H_2O . There is no NMR evidence for such a deprotonation of enamino-nitro compound **9** in C_6D_6 (see Scheme 7).

Scheme 7. *Proposed Equilibrium between the Cyclobutane 7 and an Enamino-nitronate 10* [1r]. The structure of the anion **10** was deduced from the same NMR data, which allowed us to assign the oxazine structure **8** to the species equilibrating with **7**. Unfavorable direct ring opening, **J**, of the cyclobutane. When the solution of **9** was treated (by us) with **1**, no nitronate was generated (no change of the NMR spectrum within 10 h), see also *Footnote 13*.



The rather far-reaching conclusions drawn in [1r], concerning the catalytic cycle of amine-catalyzed *Michael* additions of aldehydes to nitro olefins, require revision.

Full experimental details of our investigations, together with more examples of isolation and identification of intermediates in this type of reactions, will be presented in a forthcoming full paper [9].

We are grateful to Prof. *D. Blackmond* for pointing out to *D. S.* that there was an error in the discussion of the kinetics of the various reactions of zwitterion **D** in our original manuscript (corrected at the galley-proof stage).

REFERENCES

- [1] a) K. C. Brannock, A. Bell, R. D. Burpitt, C. A. Kelly, *J. Org. Chem.* **1964**, 29, 801; b) M. E. Kuehne, L. Foley, *J. Org. Chem.* **1965**, 30, 4280; c) A. Risaliti, M. Forchiassin, E. Valentin, *Tetrahedron Lett.* **1966**, 7, 6331; d) H. Feuer, A. Hirschfeld, E. D. Bergmann, *Tetrahedron* **1968**, 24, 1187; e) A. T. Nielsen, T. G. Archibald, *Tetrahedron* **1970**, 26, 3475; f) E. Valentin, G. Pitacco, F. P. Colonna, *Tetrahedron Lett.* **1972**, 13, 2837; g) F. P. Colonna, E. Valentin, G. Pitacco, A. Risaliti, *Tetrahedron* **1973**, 29, 3011; h) F. Felluga, P. Nitti, G. Pitacco, E. Valentin, *Tetrahedron* **1989**, 45, 5667; i) F. Felluga, P. Nitti, G. Pitacco, E. Valentin, *J. Chem. Soc., Perkin Trans. 1* **1992**, 2331; j) D. Seebach, J. Goliński, *Helv. Chim. Acta* **1981**, 64, 1413; k) S. J. Blarer, W. B. Schweizer, D. Seebach, *Helv. Chim. Acta* **1982**, 65, 1637; l) S. J. Blarer, D. Seebach, *Chem. Ber.* **1983**, 116, 3086; m) D. Seebach, A. K. Beck, J. Goliński, J. N. Hay, T. Laube, *Helv. Chim. Acta* **1985**, 68, 162; n) D. Seebach, M. Missbach, G. Calderari, M. Eberle, *J. Am. Chem. Soc.* **1990**, 112, 7625; o) M. P. Lalonde, Y. Chen, E. N. Jacobsen, *Angew. Chem.* **2006**, 118, 6514; *Angew. Chem., Int. Ed.* **2006**, 45, 6366; p) X.-j. Zhang, S.-p. Liu, J.-h. Lao, G.-j. Du, M. Yan, A. S. C. Chan, *Tetrahedron: Asymmetry* **2009**, 20, 1451; q) J. Burés, A. Armstrong, D. G. Blackmond, *J. Am. Chem. Soc.* **2011**, 133, 8822; r) J. Burés, A. Armstrong, D. G. Blackmond, *J. Am. Chem. Soc.* **2012**, 134, 6741; s) K. Patora-Komisarska, M. Benohoud, H. Ishikawa, D. Seebach, Y. Hayashi, *Helv. Chim. Acta* **2011**, 94, 719.

- [2] R. Huisgen, *Acc. Chem. Res.* **1977**, *10*, 117; R. Huisgen, *Acc. Chem. Res.* **1977**, *10*, 199; G. Urrutia-Desmaison, R. Huisgen, H. Nöth, *Helv. Chim. Acta* **2012**, *95*, 1; G. Urrutia Desmaison, R. Huisgen, H. Nöth, *Helv. Chim. Acta* **2012**, *95*, 673; R. Huisgen, G. Urrutia Desmaison, *Helv. Chim. Acta* **2012**, *95*, 1049.
- [3] M. Brenner, D. Seebach, *Helv. Chim. Acta* **1999**, *82*, 2365; D. Seebach, M. Brenner, M. Rueping, B. Schweizer, B. Jaun, *Chem. Commun.* **2001**, 207; D. Seebach, M. Brenner, M. Rueping, B. Jaun, *Chem. – Eur. J.* **2002**, *8*, 573.
- [4] J. Duschmalé, H. Wennemers, *Chem. – Eur. J.* **2012**, *18*, 1111.
- [5] Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284; *Angew. Chem., Int. Ed.* **2005**, *44*, 4212; J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296.
- [6] L. Guo, Y. Chi, A. M. Almeida, I. A. Guzei, B. K. Parker, S. H. Gellman, *J. Am. Chem. Soc.* **2009**, *131*, 16018.
- [7] Y. A. Khomutova, V. O. Smirnov, H. Mayr, S. L. Ioffe, *J. Org. Chem.* **2007**, *72*, 9134.
- [8] D. Seebach, I. M. Lyapkalo, R. Dahinden, *Helv. Chim. Acta* **1999**, *82*, 1829.
- [9] X. Sun, T. Mukaiyama, M. Benohoud, J. Duschmalé, A. K. Beck, M.-O. Ebert, W. B. Schweizer, H. Wennemers, Y. Hayashi, D. Seebach, *Helv. Chim. Acta*, in preparation.

Received May 31, 2012