Stoichiometric Reactions of Enamines Derived from Diphenylprolinol Silyl Ethers with Nitro Olefins and Lessons for the Corresponding Organocatalytic Conversions – a Survey[1])

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Dedicated to *Jack D. Dunitz* – friend and 'professor for the professors' of LOC – on the occasion of his 90th birthday

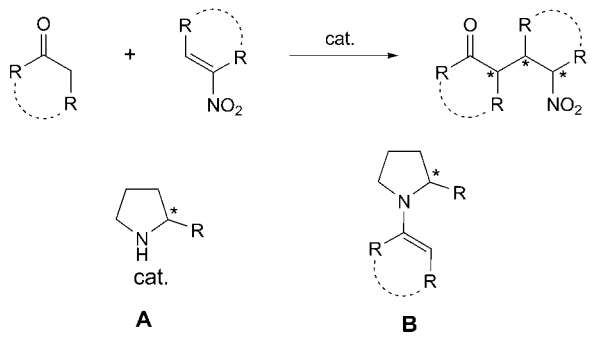
The stoichiometric reactions of enamines prepared from aldehydes and diphenyl-prolinol silyl ethers (intermediates of numerous organocatalytic processes) with nitro olefins have been investigated. As reported in the last century for simple achiral and chiral enamines, the products are cyclobutanes (**4** with monosubstituted nitro-ethenes), dihydro-oxazine *N*-oxide derivatives (**5** with disubstituted nitro-ethenes), and nitro enamines derived from γ-nitro aldehydes (**6**, often formed after longer reaction times). The same types of products were shown to be formed, when the reactions were carried out with peptides H-Pro-Pro-Xaa-OMe that lack an acidic H-atom. Functionalized components such as alkoxy enamines, nitro-acrylates, acetamido-nitro-ethylene, or hydroxylated nitro olefins also form products carrying the diphenyl-prolinol silyl ether as a substituent. All of these products must be considered intermediates in the corresponding catalytic reactions; the investigation of their chemical properties provided useful hints about the rates, the conditions, the catalyst resting states or irreversible traps, and/or the limitations of the corresponding organocatalytic processes. High-level DFT and MP2 computations of the structures of alkoxy enamines and thermodynamic data of a cyclobutane dissociation are also described. Some results obtained with the stoichiometrically prepared intermediates are not compatible with previous mechanistic proposals and assumptions.

[1]) Part of the results described herein had been reported in a preliminary communication [1].

[2]) [a]) Postdoctoral fellow at ETH Zürich 2011/12, partially financed by *Swiss National Science Foundation* (SNF-No. 200020-126693). All the isolations of intermediates and preparations of single crystals, described herein, have been carried out by *X. S.* [b]) Postdoctoral fellow at ETH Zürich 2012/13. [c]) Some of the experiments were carried out by *T. M.* during a three-month stay at ETH Zürich (August – October 2012), financed by Tokyo University of Science. [d]) Postdoctoral fellow at Tokyo University of Science (2010 – 2012), financed by *JSPS* (PE10034; P10817).

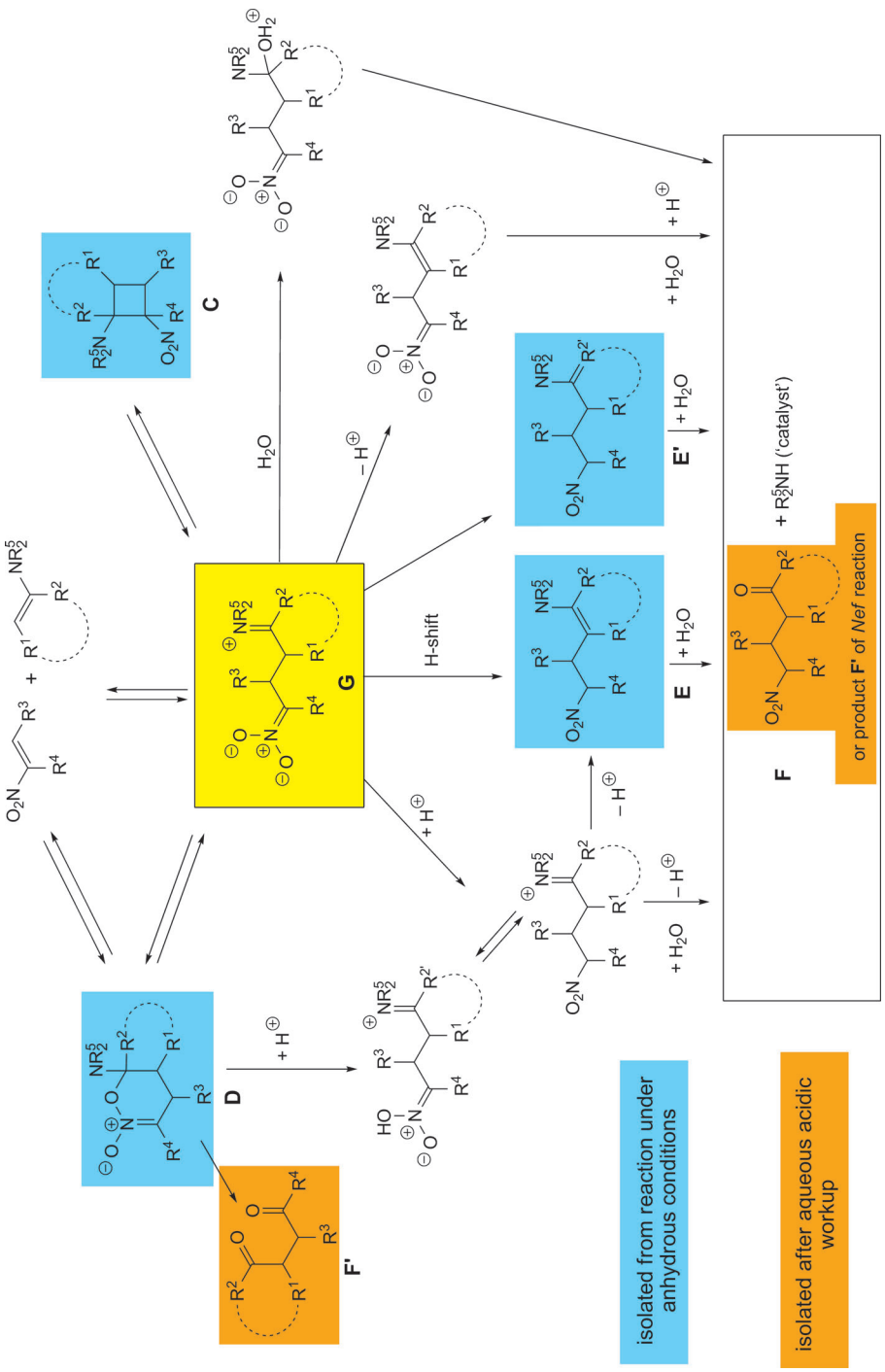
1. Introduction. – Shortly after the renaissance [2] of organocatalysis [3] had started in the year 2000, the enantioselective *Michael* addition of aldehydes and ketones to nitro olefins, catalyzed by chiral *sec*-amines, was investigated [4–6]. This type of reaction, leading to γ-nitro carbonyl compounds with up to three new stereogenic centers, became a general test track for those organocatalysts that form enamines as nucleophilic reactive intermediates (*Scheme 1*). Most of the *sec*-amino derivatives used are of the pyrrolidine type **A**[3]). The underlying reactions of chiral and achiral enamines (*cf.* **B**) with nitro olefins in stoichiometric applications have been studied in the years between 1964 and 2000 [8], and have led a rather shadowy existence. A careful study of this old literature provides the mechanistic manifold presented in *Scheme 2*. In these stoichiometric reactions, a mono- or disubstituted enamine and a nitro olefin are mixed under anhydrous conditions in an aprotic solvent such as MeCN, Et_2O, or hexanes, often with cooling, to give, after non-aqueous workup, either a cyclobutane **C** (preferentially with monosubstituted nitro olefins) or an oxazine derivative **D** (preferentially with disubstituted nitro olefins), or a nitro enamine, **E**/**E′**. All of these – isolable – primary products, **C**–**E**, are converted to the actual *Michael* adducts **F** upon hydrolysis under acidic conditions (*cf.* $EtOH/H_2O/HCl$). Possible routes for these hydrolytic conversions, mostly already proposed in the old literature [8], are included in *Scheme 2*. The elusive iminium-nitronate zwitterion **G** plays a central role in these proposals. For the reactions of the (*E*)- and (*Z*)-1-morpholinopropene (enamines from propanal and morpholine) with nitrostyrene, and of (*E*)- and (*Z*)-nitrostyrene with morpholino-cyclohexene (enamine from cyclohexanone and morpholine), the *Huisgen* test [9] for (2+2) cycloadditions *via* zwitterionic intermediates was positive: there is scrambling between the (*E*)- and (*Z*)-isomers, and the reaction is non-stereospecific (*Scheme 3*; see [10] and 1985 publication (with *Laube*) [8])[4]). Trapping of the

Scheme 1. sec-*Amine* (**A**)-*Catalyzed* Michael *Additions of Aldehydes and Ketones to Nitro Olefins and Enamine Intermediate* **B**



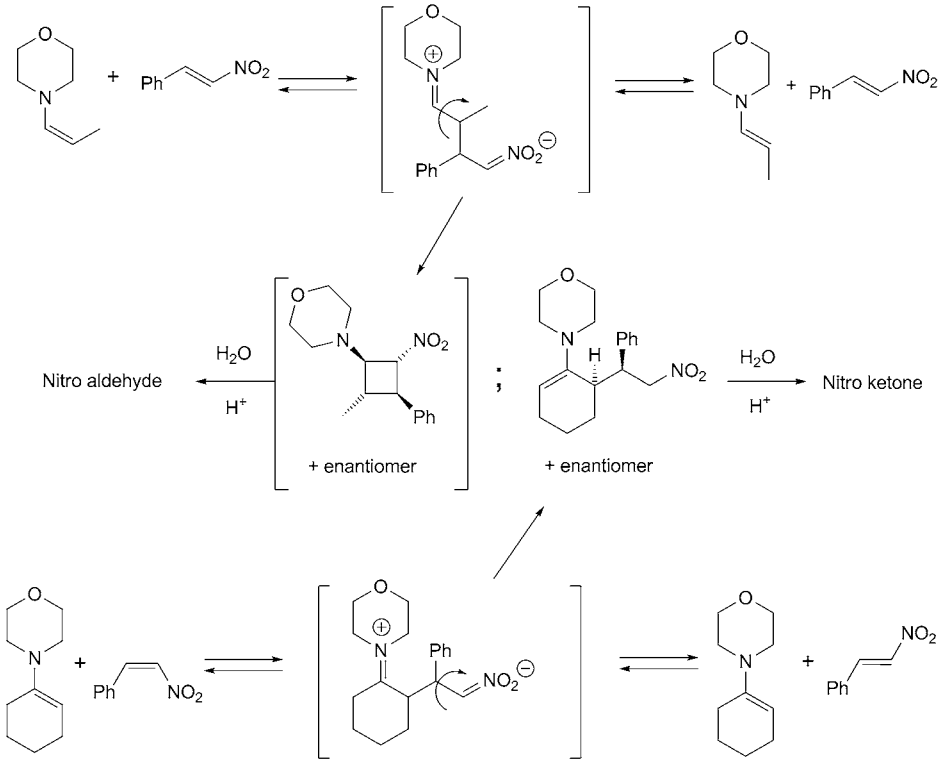
[3]) The number of reports on this type of reactions is so large (many dozens!) that we can only refer to some selected reviews [7].

[4]) In the case of the oxazine derivatives **D** (*Scheme 2*), a formally allowed [11], non-synchronous, concerted (4+2) cycloaddition, a so-called inverse-electron-demand *Diels–Alder* reaction, without a zwitterion intermediate, could be involved. In a recent *DFT calculation*, no zwitterion of type **G** was located as a low-lying energy minimum [12]. For synthetic applications and mechanistic discussions of oxazine derivatives resulting from (4+2) cycloadditions to nitro olefins of enes other than enamines (*e.g.*, enol ethers), see [13].



Scheme 2. *Possible Routes from an Enamine and a Nitro Olefin to a γ-Nitro Carbonyl Compound* **F**. Most of these routes have been proposed in the last century [8]. The formulae **D**, **C**, *and* **E**, colored blue, correspond to products isolated from stoichiometric reactions of enamines with nitro olefins under anhydrous aprotic conditions, and their acidic hydrolyses lead to nitro carbonyl compounds **F**. For the role of the zwitterionic iminium nitronate **G**, see also *Scheme 3*. Instead of the nitro carbonyl compounds **F**, *i.e.*, nitro ketones or aldehydes, the products **F'** of *Nef* reactions have sometimes been isolated.

Scheme 3. *Test for Zwitterionic Intermediates* [9] *in the (2+2) Cycloaddition of an* (E)*- and* (Z)*-Enamine, and an* (E)*- and* (Z)*-Nitro Olefin*. The same results (yield, diastereoselectivity) were obtained with the (*E*)- and (*Z*)-starting materials (see 1985 paper with *Laube* in [8], and [10]).



zwitterion in the course of aqueous hydrolysis has been considered crucial for the cyclobutane **C** to be converted to the nitro carbonyl compound **F**, while the dihydro-oxazine *N*-oxide **D**, a cyclic nitronate ester, could also undergo acidic hydrolysis to an iminium-nitronic acid or nitro iminium ion[5]) without the intermediacy of a zwitterion[6]). Except on route **G** → **E** → **F**, the absolute (with chiral enamines) and relative configurations of the two stereogenic centers (bearing R^1 and R^3) in α- and β-position

[5]) This was suggested by us (Footnote 5 in [1]) as an alternative to other 'exits' from the cyclic intermediate **D** to open-chain precursors of the final nitro carbonyl compound **F**. *Computational* results by *Pihko* and co-workers [12] indicate that protonation of an oxazine derivative of type **D** in the 3-position of the heterocycle is 'clearly favored kinetically' (*vide infra Footnote 38*), generating a nitro-alkane moiety; we are unable to judge whether the alternative protonation on O^-, with subsequent formation of a nitronic acid group, has been probed in this computational analysis. Results of deuterolysis experiments are not compatible with *C(3)*-protonation (see *Scheme 10,e*).

[6]) Rather than simple hydrolysis to the nitro carbonyl derivative of type **F**, *Nef* reactions have been observed to occur during acidic hydrolyses of the primary products (*cf. Valentin* and co-workers in [8], as well as *Yoshikoshi* and co-workers in [13]).

to C=O in **F** are set in the coupling step between the trigonal centers of the enamine and the nitro-olefin component[7]).

All the products shown (in orange and blue) and all the processes outlined in *Schemes 2* and *3* for the stoichiometric reactions between enamines and nitro olefins must be considered for the *sec*-amine-catalyzed addition of aldehydes and ketones to nitro olefins presented in *Scheme 1*. At the beginning of the competitive run in enantioselective organocatalysis, there was no time for mechanistic investigations, so that no or only a simplistic catalytic cycle[8]) was proposed, focusing on the relative topicity of the primary C,C-bond formation [4–7][7])[8]).

Intrigued by the observation that the addition of aldehydes to nitro olefins, catalyzed by the diphenyl-prolinol silyl ethers **1a** and **1b** under standard conditions (5 mol-% **1**, 5 mol-% 4-nitrophenol, 24 h, room temperature) [14], appeared to be subject to steric hindrance, resulting from the size and the number of substituents on the two reactants (an effect which had not been noticed in the stoichiometric reactions)[9]) two of our groups (*Y. H.* and *D. S.*) decided to study the addition of **1**-derived enamines to various nitro olefins under stoichiometric, anhydrous conditions[10])[11]). In this work, we present hitherto unpublished (experimental) details and case studies, which show that, for the catalytic reaction to take place, and for identifying the best conditions, it is useful to know the chemical properties of the intermediates involved.

2. Stoichiometric Reactions of Enamines, Derived from the Diphenylprolinol Silyl Ethers 1 and Aldehydes, with Mono- and Disubstituted Nitro Olefins. – We prepared solutions, in dry (D_6)benzene or (D_8)toluene, of enamines **2** (formed immediately[12])) from aldehydes and the pyrrolidines **1**, removing H_2O with molecular sieves[13]) (*Scheme 4*). The solution of the enamines was then mixed with the nitro olefin, dissolved in the same solvent, and NMR spectra were recorded immediately and after certain periods of time. In fact, and as expected, the three types of products identified and reported in the old literature (*Scheme 2*) were detected by NMR analysis: the cyclobutanes **4** (*Fig. 1*; *cf.* **C**) the dihydro-oxazine *N*-oxides **5** (*Fig. 2*; *cf.* **D**), and the nitro enamines **6** (*Fig. 3*; *cf.* **E**). The ratio depended upon the particular pair of reactants **2** and **3**, upon the temperature, and upon the reaction time, with the

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7) Following the general '*Topological Rule for C,C-Bond Forming Processes*' involving coupling of two trigonal centers (see 1981 publication (with *Golinski*) in [8]).

8) See, *e.g.*, Scheme 1 in [14] and refs. cit. therein.

9) In fact, when mixing enamines with nitro olefins an exothermic reaction takes place, so that cooling or starting the reaction at dry-ice temp. is sometimes recommended [8].

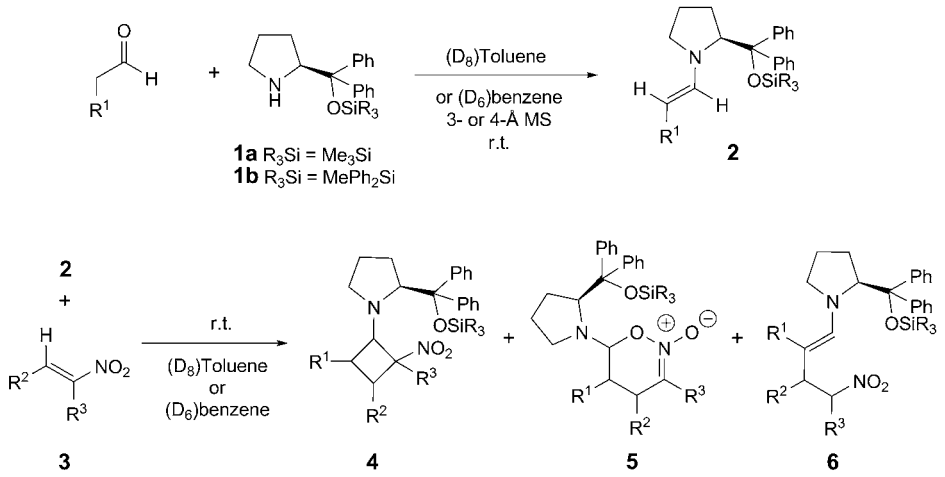
10) See [14] and the preliminary communication [1]. In the original work of *Hayashi et al.*, no acid additive was used, and the solvent was hexane [15].

11) For independent works along these lines, see [12][16][17]. For early mechanistic studies on the catalytic reaction, see *Sect. 3* and refs. cit. therein.

12) In all cases, the enamine had formed completely after a few minutes ('before we arrived at the NMR machine for recording the spectrum').

13) In the case of propanal, an excess aldehyde had to be employed to achieve complete conversion in the presence of 4-Å molecular sieves (MS), but not with 3-Å MS. We interpret this observation by assuming that propanal can enter the cavities of 4-Å but not of 3-Å MS.

Scheme 4. *Preparation of Enamine* **2** *Solutions from Aldehydes and Pyrrolidines* **1**, *and Reactions with Nitro Olefins* **3** *with Formation of Mixtures of Cyclobutanes* **4**, *Dihydrooxazine* N-*Oxides* **5**, *and Nitro Enamines* **6**. Cyclobutanes are preferred with monosubstituted nitro olefins, and oxazine derivatives are preferred with disubstituted nitro olefins, and nitro enamines are often the major products after longer periods of time.



cyclobutane **4** prevailing with monosubstituted nitro olefins, the heterocycle **5** being the only product detected with disubstituted nitro olefins, and the nitro enamine **6** often becoming the major product after extended periods of time. Equilibria between the four- and the six-membered rings, and between these cyclic compounds and the starting materials, enamine and nitro olefin, were observed. As will be discussed in the following *Sections* in detail, some of the four- and six-membered-ring compounds **4** and **5** are stable in solution at up to 50°, or even to 100°, and in five cases crystalline samples, suitable for single-crystal X-ray structure determination, could be prepared (*Fig. 4*)[14]). Most of the NMR data of compounds **4**, **5**, and **6**, presented in the *Exper. Part*, have been obtained by analysis of the complex spectra of mixtures of – sometimes equilibrating – compounds, using 2D-COSY, NOSY, HSQC, and EXSY techniques[15])[16]).

2.1. *The Cyclobutanes* **4**. As we had expected, cyclobutanes, **4a**–**4q**, are always formed from the enamines **2** and the monosubstituted nitro olefins **3** ($R^3 = H$), not only in those cases, in which the corresponding catalytic reaction under our standard conditions (toluene, room temperature, 5 mol-% **1a**, 5 mol-% 4-nitrophenol, up to 48 h; *Scheme 1*) [14] takes place (*cf.* **4a**–**4j** in *Fig. 1*), but also with the sterically more hindered reactants (*cf.* **4k**–**4q** in *Fig. 1*). The reaction becomes slower with increasing

[14]) As can be seen from *Fig. 4* of the crystal structures, the virtual electron pair on the pyrrolidino N-atom is in all cases *antiperiplanar* to the most polar C–C–N (**4q**) and C–O–N (**5b**–**5d** and **5g**) bond within the ring, as if the molecules would be ready for opening up to zwitterions in a stereoelectronically assisted process.

[15]) See Figs. 1–3 and Scheme 6 in our preliminary communication [1].

[16]) The isolation and characterization of the cyclobutanes **4e** and **4q** have been described in our previous paper [14]; improved procedures are presented herein.

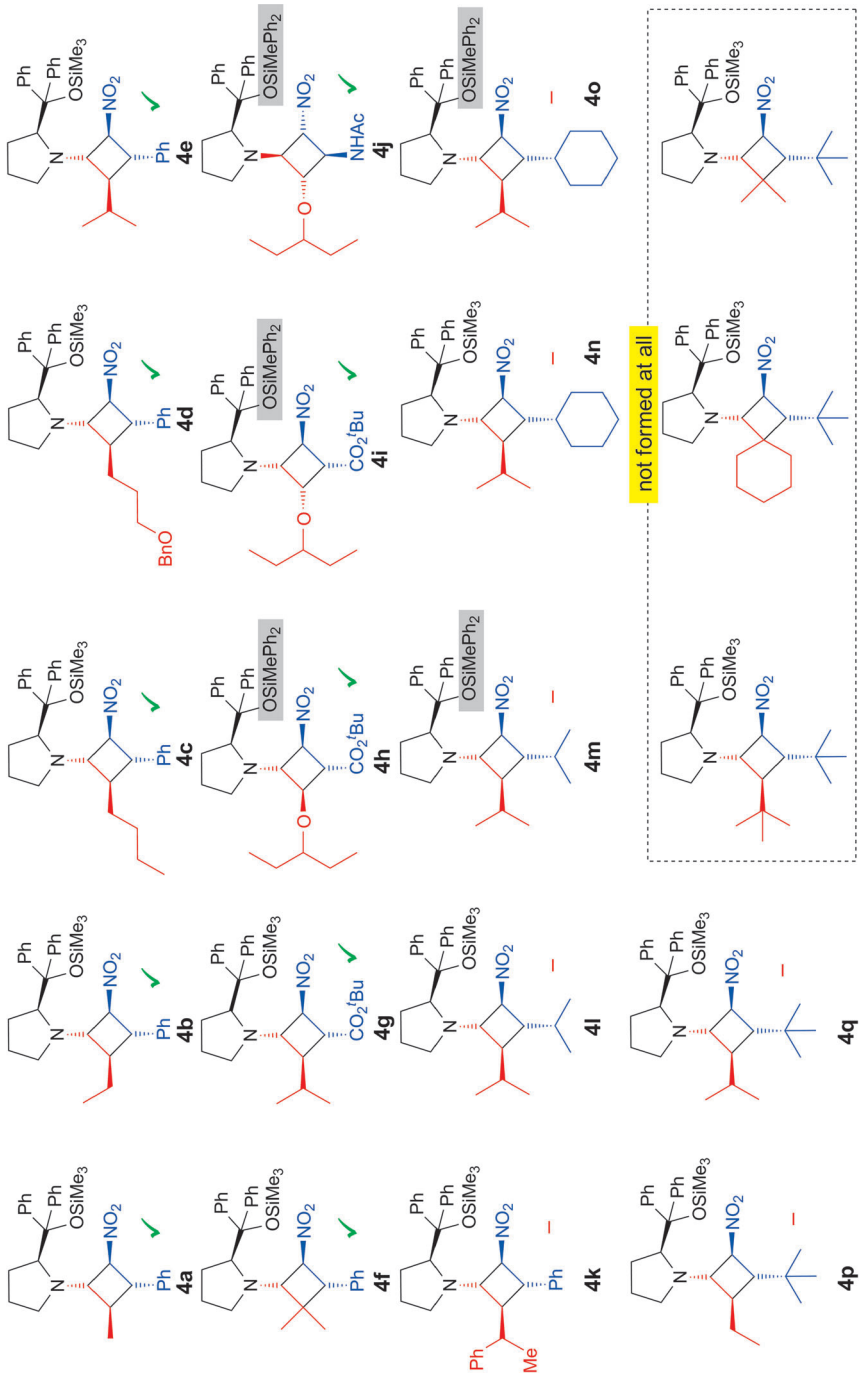


Fig. 1. *Characterized (2 + 2) cycloadducts* **4** *obtained from pyrrolidino-enamines* **2** *and nitro olefins* **3** (R^3 = H). The compounds were generated as outlined in *Scheme 4* and identified by *in situ* NMR analysis, by isolation, and in one case, *i.e.*, **4q**, by X-ray analysis (see *Exper. Part*). √, Catalytic reaction under standard conditions (toluene, 5% **1**, 5% 4-NO_2–C_6H_4OH, 24 h, room temperature) [14] takes place with the corresponding aldehyde and nitro olefin. –, No catalytic nitro-aldehyde formation with the corresponding reactants. *Box:* These cyclobutanes are not formed at all under the conditions specified in *Scheme 4*. The NMR characterization of all compounds, *i.e.*, **4a**–**4e** and **4g**–**4q**, is reported in the *Exper. Part*; for **4f**, see [16][17a].

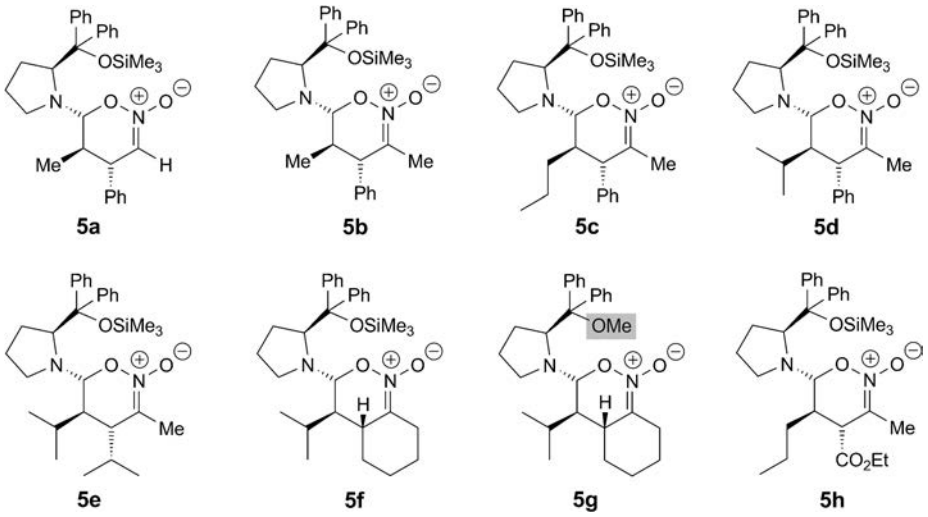


Fig. 2. *Dihydro-oxazine* N-*oxides* **5** *formed under the conditions specified in* Scheme 4. Identification by *in situ* NMR analysis, by isolation (chromatography, crystallization), and/or by X-ray crystal-structure determination (see *Exper. Part*).

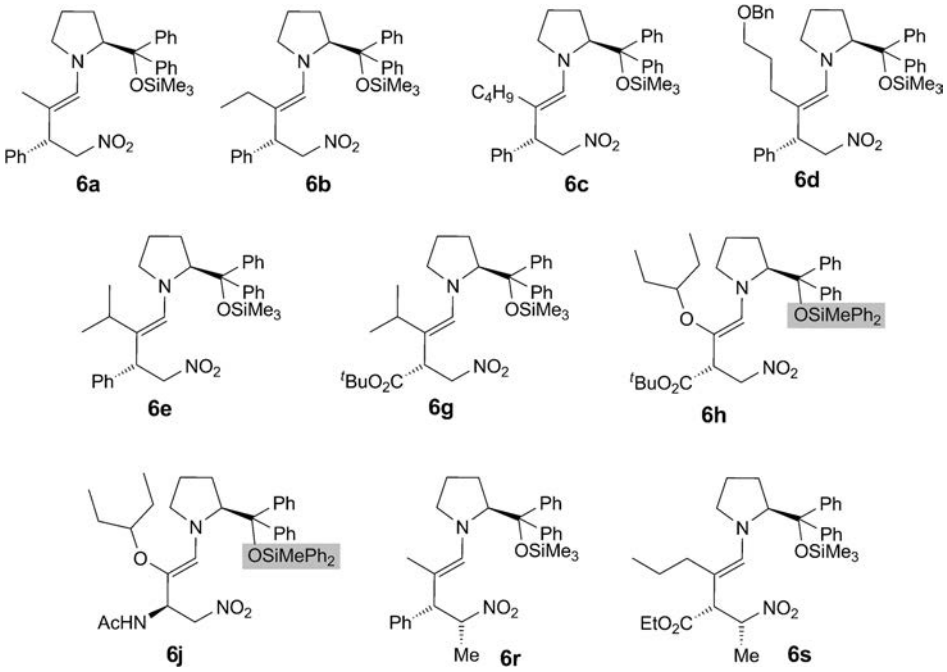


Fig. 3. *Nitro Enamines* **6** *formed, especially after prolonged reaction times, from enamines* **2** *and nitro olefins* **3** *under anhydrous conditions* (*Scheme 4*). Identification by *in situ* NMR analysis. Under carefully controlled conditions, solutions of 90% pure nitro enamine **6a** can be prepared. The letters in the compound numbering **6a**–**6j** correlate with those in *Fig. 1*.

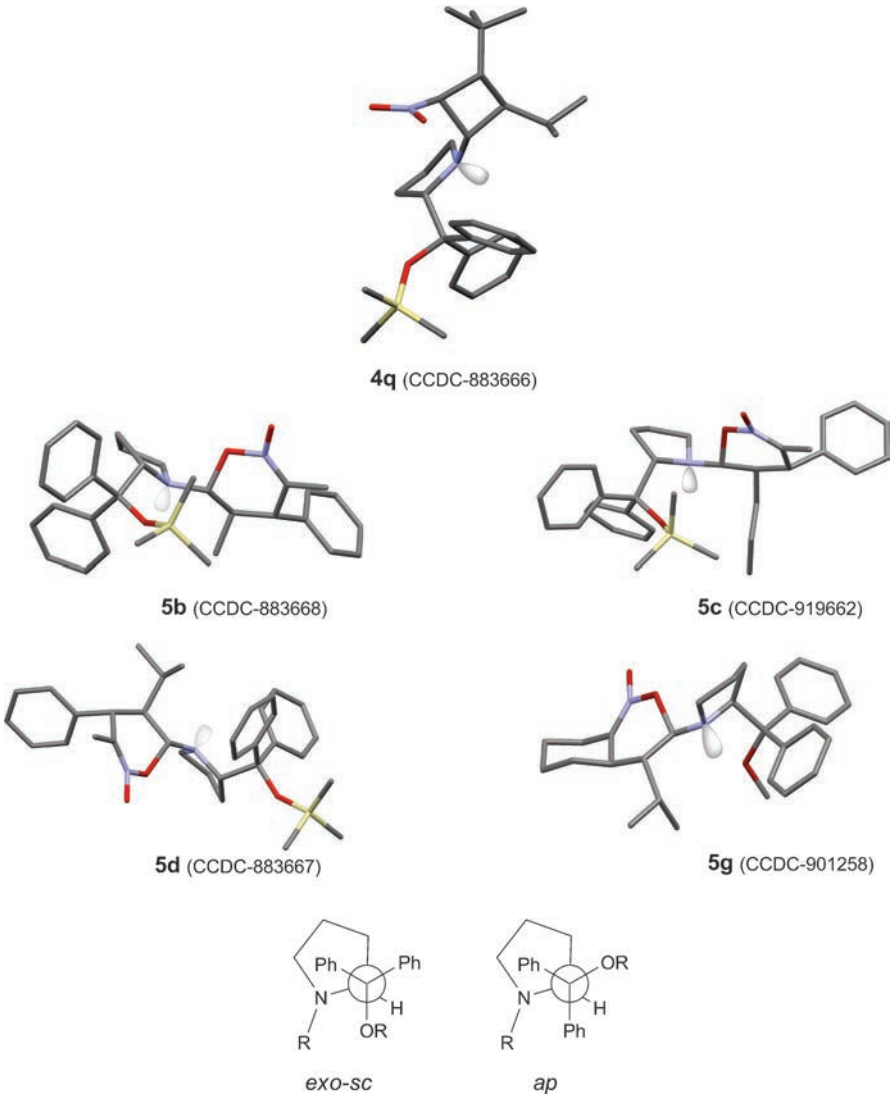
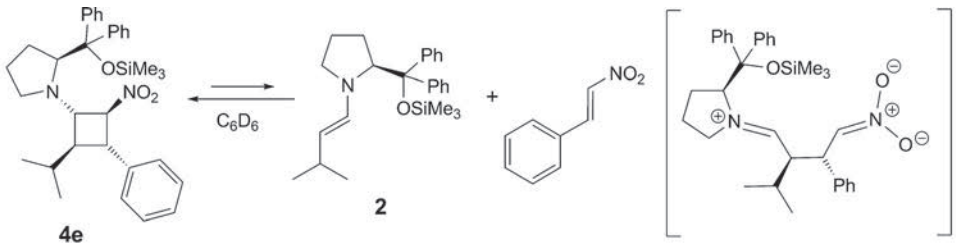


Fig. 4. *X-Ray crystal structures of the cyclobutane* **4q**, *and of the dihydro-1,2-oxazine* N-*oxides* **5b** – **5d** *and* **5g**. The structures of **4q**, **5b**, and **5d** have been reported in our preliminary communication [1]. The structure of **5g** was determined by the *Gellman* group in 2009, but submitted to the *Cambridge Crystallographic Data Centre* (*CCDC*) only recently. In all structures, there is stereoelectronic $n_N \rightarrow \sigma^*_{C,C}$ or $n_N \rightarrow \sigma^*_{C,O}$ stabilization [18a] (see also *Footnote 14*). Note that the exocyclic bond of the pyrrolidine ring has the generally preferred [18b] *exo-synclinal* conformation only in **5b**, **5c**, and **5g**, while **4q** and **5d** have the *antiperiplanar* conformation of this bond (*cf.* results of calculations in *Fig. 8* and structure of **21** in *Scheme 11*).

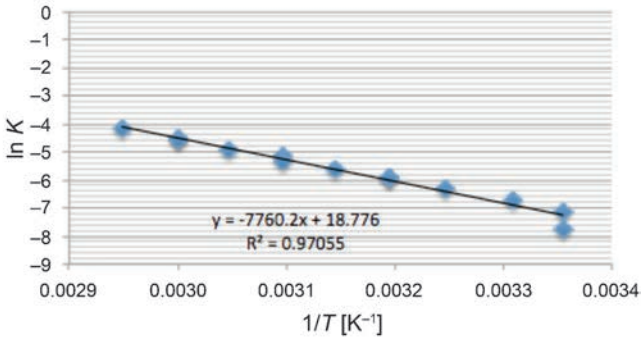
size of the substituents on the enamine and on the nitro olefin precursors, and only with too much bulk (*cf.* two ^{t}Bu groups) no cycloaddition product could be detected (see dotted-line box in *Fig. 1*). Thus, the lack of nitro-aldehyde formation under the

standard catalytic conditions with more bulky substituents is, in many cases, *not* due to lack of reactivity between the intermediate enamine and the nitro olefin.

2.1.1. *Equilibrium between a Cyclobutane of Type* **4** *and Enamine + Nitro Olefin*. A solution in C_6D_6 of the cyclobutane **4e**, prepared as shown in *Scheme 4*[17]), containing no NMR-detectable amount of oxazine **5** or nitro enamine **6** derivative[18]), but a few percent of nitrostyrene and of the enamine **2** (from 3-methylbutanal and **1a**), was stepwise heated to 66° and cooled back to r.t.; the ratio **4e**/enamine was determined by integration of suitable NMR signals after each change of temperature (for details, see *Exper. Part*). The results are presented in *Fig. 5* and show that there is a clean, fully reversible equilibrium between the (2 + 2) cycloadduct **4e** and its precursors; due to the ring strain of the cyclobutane and the necessarily large entropy factor, the cyclization is only weakly exergonic ($\Delta G = -4.3$ kcal/mol). We have not systematically looked for such equilibria with other cyclobutanes **4**, but it must be expected that they occur quite



T [°]	Concentrations [M]		
	4e	**2**	Nitrostyrene
25.0	0.185	0.004	0.037
29.1	0.183	0.006	0.038
34.8	0.181	0.008	0.042
39.9	0.178	0.011	0.043
44.9	0.175	0.014	0.045
49.8	0.171	0.018	0.056
55.0	0.167	0.023	0.055
60.2	0.161	0.028	0.061
66.0	0.154	0.035	0.068
60.2	0.161	0.028	0.060
49.8	0.172	0.017	0.050
39.9	0.178	0.011	0.045
25.0	0.187	0.002	0.039



ΔS = 156.10 J/(mol K) = 37.33 cal/(mol K)

ΔH = 64.52 kJ/mol = 15.43 kcal/mol

T = 298.15 K, ΔG = 17.98 kJ/mol = 4.30 kcal/mol

$\ln K = -\Delta H/RT + \Delta S/R$

R = 8.314 J/mol·K

1 cal = 4.182 J

Fig. 5. *Equilibrium between the amino-nitro-cyclobutane* **4e**, *and its precursors enamine and nitro olefin*. There is an excess nitro olefin in the reaction mixture (for details, see *Table 5* in *Exper. Part*). According to the NMR analysis, the solution of the equilibrating species contains no oxazine derivative **5**, and no nitro enamine **6** is detected during this experiment. The iminium-nitronate zwitterion is assumed to be involved in this equilibration process (*cf. Scheme 3*).

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17) A similar experiment, conducted with a less pure sample of **4e**, has been described in our previous paper [14].

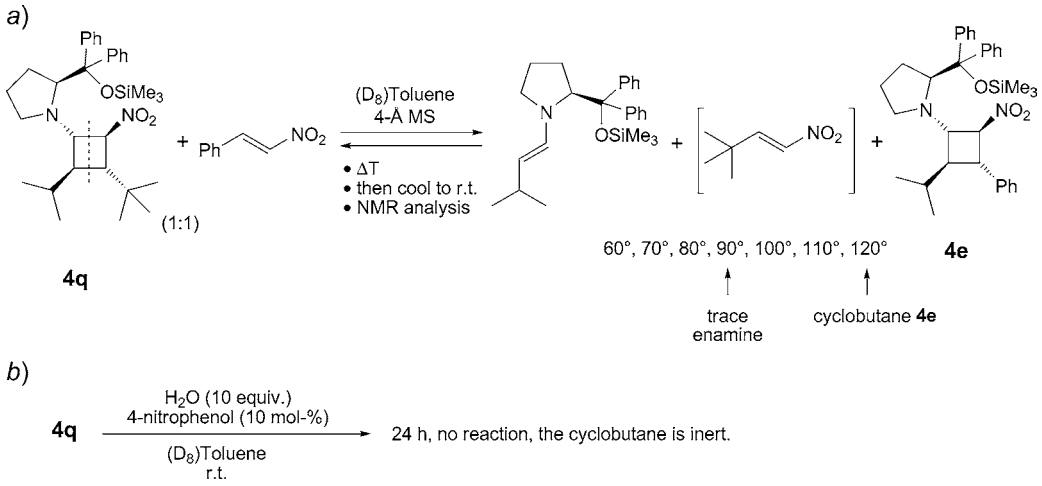
18) ... at temperatures between 25 and 66°.

generally when there is not too much bulk of substituents on the four-membered ring (*cf.* **4q**).

The *conclusion for the corresponding catalytic reaction* (in toluene, Table 4 in [14]) would be that a *zwitterion* of type **G** is an intermediate *en route* from the cyclobutane to the open-chain nitro aldehyde of type **F**[19]).

2.1.2. *Stability of Cyclobutane* **4q**. Our most stable *amino-nitro-cyclobutane* **4q** (*Fig. 4* and *Footnote 16*) was prepared from the ^{t}Bu-substituted nitro-ethene and the ^{i}Pr-substituted enamine as outlined in *Scheme 4*; formation of **4q** took 3 d in (D_6)benzene (85% yield after crystallization; m.p. 138–144° (dec.)) and 18 h in the presence of 1 equiv. 4-nitrophenol[20]). To test the thermal stability of this cyclobutane, we heated its solution in (D_8)toluene in the presence of 1 equiv. of nitrostyrene (*i.e.*, (*E*)-*β*-nitrostyrene; sealed NMR tube). The result is outlined in *Scheme 5:* up to 80°, nothing happened; at 90°, we identified traces of the enamine precursor, and after heating to 120° the cyclobutane **4e** (product of scrambling) was detected. When the solution of **4q** was kept at room temperature in the presence of 4-nitrophenol and H_2O, there was no product of hydrolysis after 24 h; addition of acidic alumina (activity grade 1) or of $ClCH_2CO_2H$ to the $CHCl_3$ solution, or chromatography of **4q** on silica gel did not lead to the corresponding nitro enamine or nitro aldehyde.

Scheme 5. *Thermal and Hydrolytic Stability of the Cyclobutane* **4q** *in (D₈)Toluene. a*) The solution containing 1 equiv. of nitrostyrene was heated for 30 min at the indicated temperature in a sealed NMR tube, and, after cooling to ambient temperature, the spectra were recorded. The cyclobutane **4e** (with 'exchanged' nitro olefin-derived part of the molecule) is detected only after heating above 100°. *b*) The mixture containing 10 equiv. of H_2O and 4-nitrophenol was kept at r.t. (*cf.* the catalytic conditions [1][14]): no NMR-detectable trace of the corresponding nitro aldehyde was formed under these conditions. For other tested hydrolysis/decomposition conditions, see accompanying text.



[19]) See the article by *R. Huisgen* entitled '*Can Tetramethylene Intermediates Be Intercepted?*' [9b].

[20]) Acid additives are essential for effective catalysis of the *Michael* addition of carbonyl compounds to nitro olefins (*Scheme 1*); see discussions and references in [7][14] and in [19].

The *conclusion for the reaction under our standard catalytic conditions* would be that the (2 + 2) cycloadduct is slowly formed, but is not opening up to a linear intermediate to give the nitro aldehyde; in this case, the cyclobutane is a dead-end trap for the pyrrolidine catalyst.

2.1.3. *Equilibrium between Cyclobutane* **4a** *and Oxazine Oxide Derivative* **5a**. In an elaborate NMR analysis, we have found that the reaction between the propanal enamine and nitrostyrene in (D_6)benzene leads to an equilibrating mixture of the cyclobutane **4a** and the oxazine *N*-oxide **5a** (4 : 1 ratio at room temperature), which is converted to the nitro enamine **6a** within 15 h; in CH_2Cl_2 solution the open-chain compound is formed within 10 min (*Scheme 6*) [1]. This was recently confirmed by an independent investigation by *Pihko* and co-workers (propanal/nitrostyrene/**1a** 1 : 1 : 2, (D_8)toluene, room temperature, complete conversion in 24 h)[21]). A reasonable mechanism for the equilibration **4a** ⇌ **5a** and for the conversion **4a**/**5a** → **6a** would be formation of the zwitterion and an intra-[22]) or intermolecular H-shift, which was confirmed by the D-labeling experiment outlined in *Scheme 6*, *b*.

2.1.4. *Acid Hydrolysis of the Nitro Enamine* **6a** *to the Nitro Aldehyde* **7a**. Under the conditions indicated in *Scheme 6*, *a*, we could prepare rather pure samples of the nitro enamine **6a** (84% on an 0.5-g scale), which we used to probe the diastereoselectivity of the acidic hydrolysis to the nitro aldehyde **7a** under two sets of conditions (*Scheme 7*): similar to the catalytic reaction [14], a 0.05M solution of **6a**, 1 equiv. 4-nitrophenol, and 1 equiv. H_2O in benzene was kept at room temperature for up to 40 h, and similar to the classical workup of stoichiometric reactions of enamines with nitro olefins [8], **6a** was dissolved in EtOH and treated with H_2O/HCl. As can be seen from the data in the table of *Scheme 7*, the selectivities determined by NMR analysis are poor (≤ 3 : 1), as compared to those of the corresponding catalytic reaction providing the diastereoisomer **7a** with a dr of 15 : 1 [14]. *Burès et al.* [17a] have performed a kinetic analysis of the reverse reactions (**7a** + **1a** ⇌ **6a** + H_2O and *epi*-**7a** + **1a** ⇌ **6a** + H_2O) from which they calculated a protonation selectivity of ≥ 39 : 1; they concluded that the configuration of the center bearing the Me group is not set in the coupling step of the trigonal centers of enamine and nitro olefin, but in the nitro enamine protonation step and modified the catalytic cycle accordingly. We are unable to interpret the discrepancies between these experimental results, *i.e.*, the diastereoselectivities of the *catalytic* reaction without added acid (14 : 1 [14]) or with 4-nitrophenol (15 : 1 [14]), the *stoichiometric* reaction with 4-nitrophenol (3 : 1) or with HCl (1.5 : 1) (*Scheme 7*), and the kinetics of equilibration between the diastereoisomers **7a** and *epi*-**7a** with **1a** (39 : 1 [17a]); an expert physical-chemical analysis is required[23]).

2.1.5. *Reactions of Enamines from 2-Alkoxyacetaldehyde with 3-Nitroacrylate* (= *(*E*)-3-Nitroprop-2-enoate*) *and 2-Acetamido-nitroethene*. These reactants have been used for syntheses of oseltamivir, the active agent of the antiviral drug *Tamiflu*® [21 –

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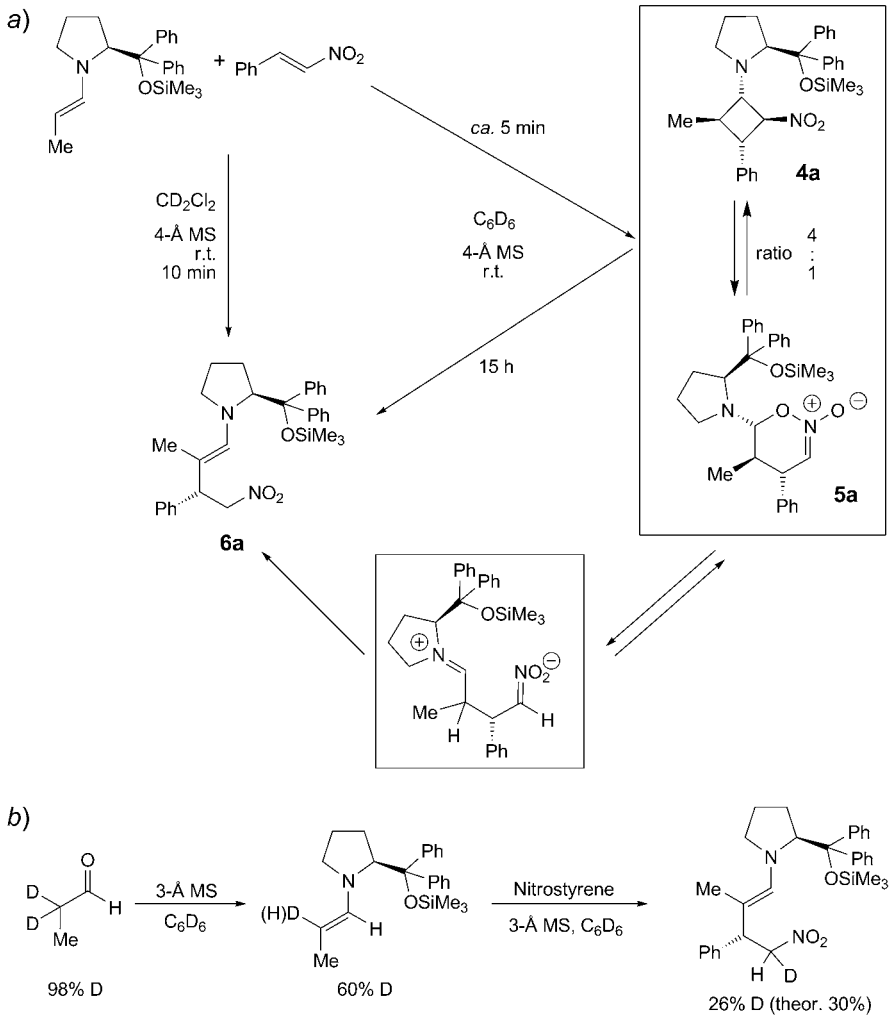
[21]) See Fig. 2 in [12] (received June 20, revised October 10, and published online November 11, 2012); *cf.* also [17]; [1] was received May 31, and published online July 11, 2012.

[22]) See also Scheme 1 in [1].

[23]) Protonation, deprotonation, and iminium-ion formation are involved in the reaction between a *sec*-amine and an aldehyde, as well as in the reverse reaction, the hydrolysis of an enamine; in the reactions discussed here, the protonating species may be H_3O^+, $EtOH_2^+$, 4-nitrophenol, $R_2^*NH_2^+$.

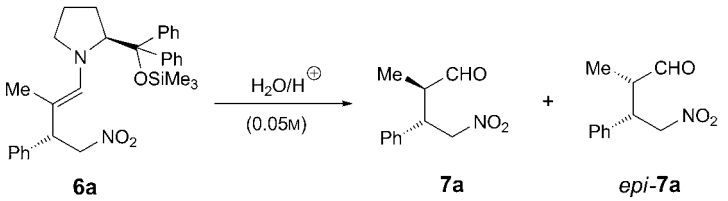
Scheme 6. *Equilibrium between the Nitrocyclobutane* **4a** *and Its Six-Membered-Ring Isomer* **5a**, *and Rearrangement to the Nitro Enamine* **6a**. The NMR spectra for the detection of this process are shown and the detailed analysis is described in [1]. *a*) Slow ring opening in benzene, fast ring opening in CH_2Cl_2 with the corresponding zwitterion as presumed intermediate. *b*) With D-labeled enamine, the label ends up in the α-NO_2 position. For a possible intramolecular H-shift converting the zwitterion to the nitro enamine, see Scheme 1 in [1]. For a preparation of the dideutero-propanal, see [20].



23]. Before turning to the stoichiometric reactions of the corresponding isopentyloxy enamine, a new type of resting state of the catalyst **1a** is discussed.

2.1.5.1. *The* Michael *Adduct of* **1a** *to Nitroacrylate*. The nitroacrylate is a much more reactive *Michael* acceptor than nitrostyrenes or aliphatic nitro olefins. Indeed, when the 'catalyst' **1a** was added to a *tert*-butyl-3-nitroacrylate solution in C_6D_6 or CD_2Cl_2, the

Scheme 7. *Poorly Stereoselective Hydrolysis of the Nitro Enamine* **6a** *to the Nitro Aldehyde* **7a**. Conditions *A* as for the catalytic reaction [14]; conditions *B* are typical for the workup of stoichiometric reactions of enamines with nitro olefins [8].

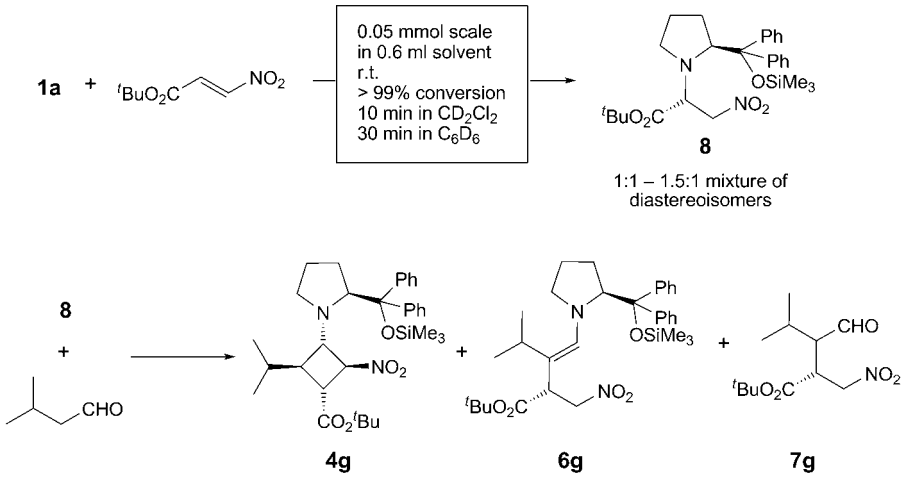


Conditions *A*: H_2O (1equiv.), 4-NO_2–C_6H_4OH (1 equiv.), C_6H_6, r.t.
B: H_2O (1 equiv.), 2N HCl (1 equiv.), EtOH, r.t.

Conditions	Time	**7a**/*epi*-**7a**	Conversion [%]
A	15 min	3.1: 1	83
A	30 min	2.7: 1	85
A	1.5 h	2.1: 1	86
A	16 h	1.5: 1	89
A	40 h	1.5: 1	89
B	10 min	1.5: 1	> 99
B	after workup	1: 1.1	

adduct **8** was formed (*Scheme 8*); in CH_2Cl_2 this took just a few minutes[24]). The reaction was reversible, *i.e.*, the adduct **8** is a resting state of the catalyst: addition of 3-methylbutanal led to the cyclobutane **4g**, and then to the nitro enamine **6g**, and finally

Scheme 8. *Addition of 'Catalyst'* **1a** *to Nitroacrylate and Reaction of the Adduct* **8** *with 3-Methylbutanal to Eventually Produce the Formyl Ester* **7g** (up to 72%; for details, see *Table 7* in the *Exper. Part*)



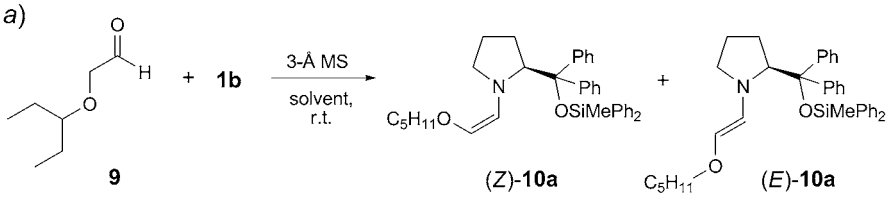
[24]) With nitrostyrene, no reaction takes place (in C_6D_6) in 24 h; *Blackmond* and co-workers mention < 5% of adduct formation, without giving experimental evidence [16]. With ethyl (*E*)-3-nitrobut-2-enoate, there is 71% conversion to the corresponding adduct in 20 h (C_6D_6, room temperature).

to the corresponding nitro aldehyde (**7g** in *Scheme 8*) over a period of hours and days (NMR analysis; for details see *Table 7* in *Exper. Part*). To consider the importance of this resting state **8** of the catalyst **1a**, we have to remember *a*) that there is a large excess of the nitro olefin *vs. sec*-amine under catalytic conditions (shifting an equilibrium towards adduct **8**), *b*) that there was always an acid co-catalyst necessary to render the catalytic reaction effective, and acid will catalyze the elimination **8** → nitroacrylate + **1a**, and *c*) that this conjugate addition was much slower with the less reactive nitro olefins.

2.1.5.2. *Reactions of* (E)/(Z)*-Pentyloxy enamines with Functionalized* (E)*- and* (Z)*-Nitro Olefins.* When the pent-3-yloxy aldehyde **9**[25]) shown in *Scheme 9* was mixed with the pyrrolidine **1b** in various dry solvents in the presence of 3-Å MS, a mixture (*Z*)/(*E*)-enamine **10a** was formed. The resulting solution in C_6D_6 of the two isomers contained an excess (up to 1.8 : 1) of the (*Z*)-form. For a theoretical analysis of this type

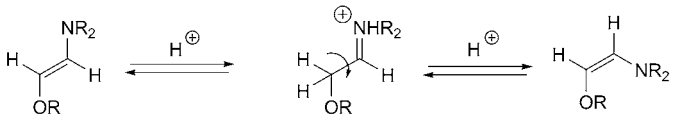
Scheme 9. *Preparation of Solutions of* (Z)/(E)*-Mixtures of Enamine* **10a** *from Aldehyde* **9**. *a*) Except in $CDCl_3$, the (*Z*)-isomer prevails slightly. There is essentially no temperature effect and only a small effect of 4-nitrophenol on the (*Z*)/(*E*)-ratio. In an EXSY-NMR spectrum, there is no cross-peak between the signals of the two isomers. We assume that the ratios are thermodynamical values, in agreement with some of the calculated energy differences between (*E*)- and (*Z*)-forms of alkoxy enamines (see the theoretical investigations of enamines of type **10** described in *Sect. 2.1.5.3* (*Fig. 8* and *Table 2*)). *b*) Under the typical catalytic conditions, there is always an acid co-catalyst present [21–23], which is expected to equilibrate the (*E*)- and (*Z*)-alkoxy enamines!

a)



	(*Z*)/(*E*) Ratio in		
	C_6D_6	C_7D_8	$CDCl_3$
after 30 min, r.t.	1.20	1.29	0.94
after 20 h, r.t.	1.61	1.76	0.92
at 70°	1.77		
with 5 mol-% 4-(NO_2)C_6H_4OH after 5 min	1.70		
7 h	1.26		

b)



[25]) For organocatalytic *Michael* additions of 2-(trimethylsilyloxy)acetaldehyde to nitro olefins, see [24].

of an alkoxy enamine, which at the same time is an amino-enol ether, a highly electron-rich system [25a–c], see *Sect. 2.1.5.3*.

Upon addition of an equimolar amount of *t*-butyl 3-nitroacrylate to the solution in C_6D_6 of the alkoxy enamine **10a** ((*Z*)/(*E*) *ca.* 1.5:1), the highly electrophilic nitro compound disappeared completely and immediately (*Fig. 6*). The two stereoisomeric cyclobutanes **4i** (formally derived from (*Z*)-**10a**) and **4h** (from (*E*)-**10a**) were formed in a ratio of *ca.* 1:2, and very little nitro enamine **6h** was detected in the initial NMR analysis. Over a period of *ca.* 50 min, the fraction of the cyclobutane (**4i**), derived from (*Z*)-enamine, decreased, and the ratio of the five components of the mixture remained more or less constant (an equilibrium situation?), with the (*Z*)/(*E*)-enamine ratio still being close to 1.5:1, and the ratio all-*trans*/*cis*,*cis*,*trans*,*trans*-cyclobutane, *i.e.* **4h**/**4i**, being *ca.* 8:1; the nitro enamine (**6h**) concentration had somewhat increased at this point, more or less at the expense of the minor cyclobutane **4i**. Four points are worth emphasizing: *a*) in the instantaneous ($\leq$5 min) reaction of the electron-rich alkoxy enamine with the electron-poor nitroacrylate, both enamines reacted, but there was twice as much product (*i.e.*, **4h**) derived from the minor enamine isomer ((*E*)-**10a**); *b*) the concentration of the all-*trans*-cyclobutane, **4h**, was constant after the first 'flash' reaction; *c*) the corresponding catalytic reaction gave best results when carried out in toluene and in the presence of $ClCH_2CO_2H$ (yield of nitro aldehyde > 99%, dr 7.8:1, er 98.5:1.5) [14][21]; *d*) an epimerization on the RO-substituted center of **4i** to give **4h** would require dissociation back to the *cis*-enamine and *cis*/*trans*-isomerization thereof (*cf. Scheme 9*).

In any case, it looks as if *the success of the catalytic reaction* is the result of a complex series of steps involving various species, possibly including the resting state **8** (*Scheme 8*), and not just a simple preference of the transition state/zwitterion **H** (bottom part of *Fig. 6*)[26])[27]).

The stoichiometric reaction between the (*E*)/(*Z*)-enamines **10a** and acetamido-nitro-ethene took an even more surprising course (*Fig. 7*). The nitro compound is less reactive than nitroacrylate; (*Z*)-enamine **10a** reacts faster than the (*E*)-enamine. Besides the open-chain nitro enamine **6j** only one cyclobutane, the 'all wrong' *all-trans*-compound **4j** was formed, and not the *cis-trans-cis-trans*-isomer expected from the trajectory and zwitterion/transition state **I** (*Fig. 7*). Again, a more or less stable composition of the components resulted from this stoichiometric reaction after *ca.* 1 h. We wondered whether the acetamido-nitroethene really has the *cis*-configuration, stabilized by an intramolecular H-bond, as generally assumed, and recorded its NMR spectrum in carefully neutralized $CDCl_3$ and in a series of solvents containing H-bond acceptor groups, all the way to (D_6)DMSO (the solvent of choice for breaking intra- and intermolecular H-bonds, by being an excellent H-bond acceptor)[28]). The results

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[26]) ... as seemed to be the case when 2-alkyl- and 2-aryloxy-acetaldehydes were added to nitro olefins (including ethyl nitroacrylate) in a less diastereoselective reaction (catalyst **1a**, toluene, room temperature, 55 or 96 h) [14][23b]; see, however, the reaction in DMSO and in $CHCl_3/H_2O$ [23a].

[27]) In the catalytic reaction, it is important to perform the workup at the right point in time to avoid erosion of the diastereoselectivity [21].

[28]) This is why we have expressed doubt [25k] about the stereodirecting role of the carboxylic acid group by H-bonding in proline catalysis of reactions carried out in DMSO [6][26].

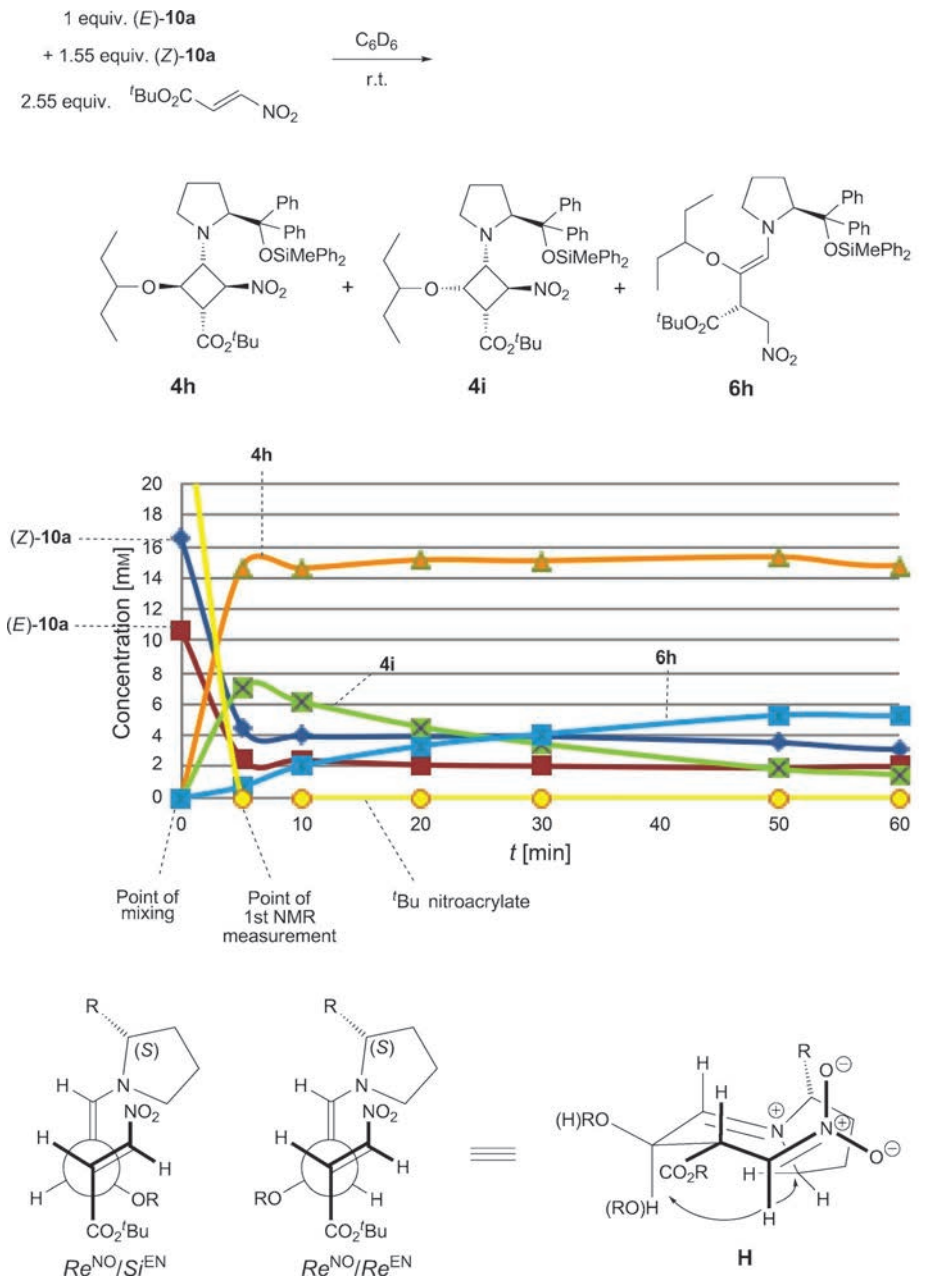


Fig. 6. *Stoichiometric reaction of the (*Z/E*)-enamine* **10a** *with (*E*)-nitroacrylate in benzene, NMR analysis of the reaction mixture, and model for the transition state/zwitterion* **H** *with least steric hindrance between the substituents* ((*E*)-enamine/(*E*)-nitroacrylate). The approach **H** would lead to the all-*trans*-cyclobutane **4h**. Epimerization **4i** → **4h** would require dissociation to the starting materials (through a zwitterion) and (*Z*/*E*)-**10a** isomerization. From the concentration traces, it looks like **6h** is actually formed from **4i**, rather than from **4h** under these conditions. Note that in our (*Y. H.*) published [21] oseltamivir synthesis *ent*-**1a** was used as catalyst (solvent toluene, co-catalyst $ClCH_2CO_2H$).

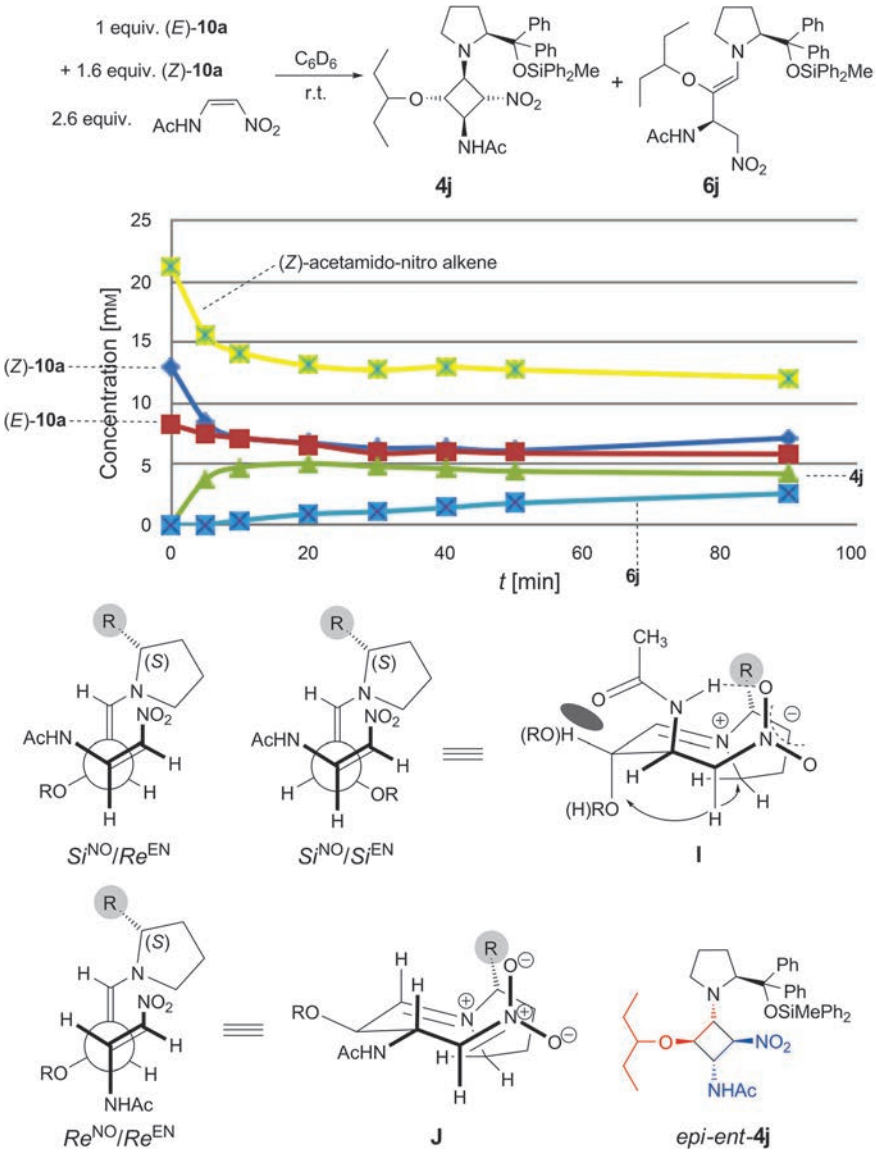
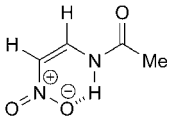
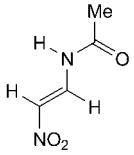


Fig. 7. *Stoichiometric reaction of the* (Z/E)*-enamine* **10a** *with* (Z)*-acetamido-nitroethene in benzene, NMR analysis of the reaction mixture, and model for the transition state/zwitterion* **I** *with least steric hindrance between the substituents* ((*Z*)-enamine/(*Z*)-nitro olefin). The approach **I** would lead to a *cis-trans-cis-trans*-cyclobutane, which is not detected. Note that the (*Re*/*Re*)-coupling (see **J**) of (*E*)-enamine with (*E*)-nitro olefin (*cf. Table 1*) would give a diastereoisomer of **4j**, in which the absolute configurations of all four stereogenic centers on the four-membered ring are reversed: *epi-ent*-**4j** (epimeric at C(2) of the pyrrolidine ring); by the NMR analysis, we could not reliably differentiate between **4j** and *epi-ent*-**4j**, for instance, from the NOE between the H-atom in α-position to NO_2 and the H–C(2) of the pyrrolidine ring (in some of the cyclobutanes **4**, this NOE is strong, in others it is absent). The *epi-ent*-**4j** cyclobutane would, of course, eventually lead to *ent*-oseltamivir! Note that, in the oseltamivir synthesis of *Ma* and co-workers [22], catalyst **1**, with $R_3Si = Me_3Si$ and naphthalenyl instead of Ph groups on the prolinol ether unit, was used. In our (*Y. H.*) recent unpublished work, the catalyst **1b** turned out to be superior to **1a**.

are compiled in *Table 1:* in 'neutral' $CHCl_3$[29]) the *cis*-isomer prevailed, in DMSO[30]) the *trans*-isomer was in excess. This means that the involvement of the *trans*-acetamido-nitroethene has to be considered in the oseltamivir syntheses using this nitro olefin derivative [21–23][31]). However, as shown in *Fig. 7* (bottom part), coupling **J** of (*E*)-enamine **10a** with the (*E*)-acetamido-nitroethene would eventually lead to *ent*-oseltamivir.

Table 1. *(*E*)/(*Z*) Ratio* [%] *of Acetamido-nitroethene in Different Solvents as Determined by NMR Spectroscopy*

Solvents		
$CDCl_3$ washed with basic Al_2O_3	> 99	< 1
(D_8)THF	80	20
CD_3OD	18	82
(D_5)Pyridine	15	85
(D_7)DMF	11	89
(D_6)DMSO	7	93

Obviously, an even more complex, most puzzling sequence of events is likely to be involved in the case of the *successful catalytic application* of isopentyloxy-acetaldehyde addition to acetamido-nitroethene (see *Fig. 7*) than in the case of addition to the nitroacrylate.

2.1.5.3. *DFT- and MP2-Calculations of the Structures of Alkoxy enamines.* The experimental observation of a (*Z*/*E*)-ratio close to 1:1 of the enamine **10a** from diphenyl-prolinol Si ether **1a** and 2-(pentyloxy)acetaldehyde prompted us[32a]) to carry out a computational investigation of alkoxy enamines, to evaluate whether the almost equal stability of these (*Z*)- and (*E*)-isomers is found for the isolated species[32b]).

Computational Methodology. For all quantum-chemical calculations, we employed the Turbomole 6.4 suite of programs [25d]. All density-functional theory (DFT) calculations applied the BP86 density functional [25e,f]. To study the method dependence of the DFT results obtained, we compared with second-order *Møller-Plesset* perturbation theory (MP2) results for selected molecules. For large molecules, MP2 calculations became less and less feasible so that the empirical D3 corrections by

29) We thank Dr. *J. Durmis* [23a,c] for a personal communication about a 10:1 *cis*/*trans* ratio of acetamido-nitroethene in $CDCl_3$.

30) In fact, the catalytic reaction used in a recent oseltamivir synthesis [23a] occurred with best diastereoselectivity in DMSO.

31) The acid co-catalyst present in all catalytic coupling reactions between 2-alkoxyacetaldehydes and acetamido-nitroethene will thus not only be able to catalyze (*Z*)/(*E*)-enamine (*cf. Scheme 9*,*b*)) but might also cause (*Z*)/(*E*)-nitro olefin equilibration.

32) [a]) Anti-intuitive '*cis*-effects' have always been intriguing for organic chemists [25a–c]. [b]) For a comprehensive review (95 pages!) entitled '*Quantum Mechanical Investigations of Organocatalysis: Mechanisms, Reactivities, Selectivities*', see [7] (*Houk* and co-workers).

Grimme et al. [25g] have been used to include dispersion effects in the DFT/BP86 calculations. All energies have been obtained after full structure optimization with the quantum-chemical method under consideration. *Ahlrichs*' basis sets of triple- (TZVPP) and quadruple-zeta (def2-QZVPP) quality, respectively, have been used as implemented in Turbomole 6.4. In these basis sets, polarization functions were taken from *Dunning*'s correlation consistent basis sets. The resolution-of-the-identity density-fitting technique has been invoked for BP86 and MP2 with the corresponding auxiliary basis sets from Turbomole 6.4 in order to accelerate the calculations. The orbitals have been tightly converged until the change in relative electronic energy in the final self-consistent field iterations step was smaller than 10^{-8} Hartree. Moreover, the structure optimization was carried out until the length of the geometry gradient was on the order of 10^{-4} atomic units. In all DFT calculations, we employed a fine numerical integration grid ('m4' in Turbomole notation).

Conformational effects can blur the energetic ordering of different isomers if alkyl substituents are present. To avoid such effects, we made sure that corresponding (*Z*)- and (*E*)-isomers always feature similar conformations of the corresponding alkyl substituents (see also below for a more detailed discussion of such effects). The energies reported are differences of electronic energies. Hence, purely electronic effects have been considered rather than zero-point-energy and temperature corrections as well as entropy effects, which we have not taken into account.

As molecules for the calculations, we chose the simple, prototypical 1-(dimethylamino)-2-methoxyethene (**10b**) and the diphenylprolinol trimethylsilyl ether-derived 1-(benzyloxy)-[33]) and 1-(isopentyloxy)-2-pyrrolidinoethenes (**10c** and **10d**, resp.). The results are collected in *Table 2* and *Fig. 8*.

Discussion. First of all, we find a more or less pronounced *pyramidalization of the N-atoms* in all calculated structures. We use *Dunitz*'s definition for the degree of pyramidalization Δ [Å] as the distance of the N-atom from the plane spanned by its three bonding partners (here C-atoms) [25h]. The Δ values (*Table 2*, last two columns) are between 0.0 and 0.3 Å[34]). For the generic small molecule **10b** that carries only Me groups as substituents, we found a BP86/TZVPP Δ value of 0.28 Å for the (*Z*)-isomer, whereas it was slightly larger (by 0.02 Å) for the (*E*)-isomer. While these Δ values increased in the MP2 calculations by 0.06 Å, the difference between the (*Z*)- and (*E*)-isomers remained the same, *i.e.*, 0.02 Å. For the isomers of **10c** and **10d** with bulky substituents, this difference increased to values between 0.03 – 0.04 Å (BP86/TZVPP). Also for the large molecules with benzyl and isopentyl substituents, the (*E*)-isomer was slightly more pyramidalized on N than the (*Z*)-isomer. It is interesting to note that the pyramidalization in **10c** and **10d** with bulky substituents is reduced when one considers attractive forces due to dispersion. As the BP86-D3/TZVPP results demonstrated, Δ was reduced by 0.10 to 0.13 Å in the *sc-exo* conformations (*Table 2*). This planarization affects the (*E*)- and (*Z*)-isomers to the same extent. However, the situation changed when the *ap*-conformations were investigated. Here, a reduced pyramidality of the N-atom was observed (because the two bulky substituents at the two ends of the molecule

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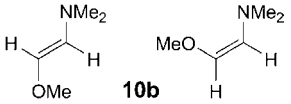
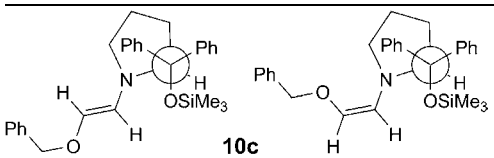
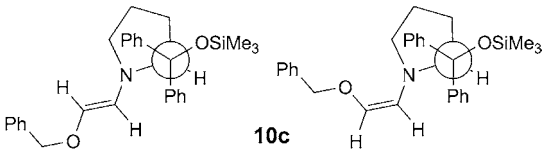
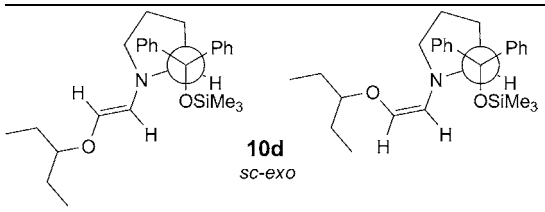
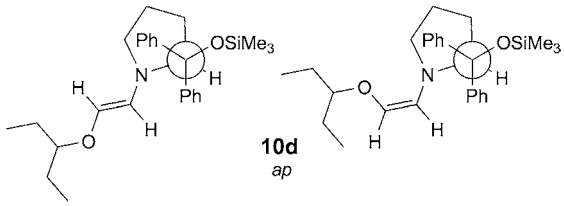
[33]) For a DFT calculation of this benzyloxy derivative, using B3LYP/6-311 + G**, see [23b] and *Table 2*.

[34]) For an sp^2-hybridized N, Δ is 0 Å; for an sp^3-hybridized N, Δ is 0.48 Å (with C,N-bond lengths of 1.45 Å).

Table 2. *Relative Energies of (*E*)- and (*Z*)-Alkoxy-enamines Calculated by DFT and MP2. Method A:* BP86/TZVPP; *Method B:* BP86-D3/TZVPP; *Method C:* MP2/def2-QZVPP; *Method D:* B3LYP/6-311 + G**. The value obtained with *Method D* is taken from [23b]. Besides the generic (dimethylamino)-methoxy-ethene, only the structures with the experimentally observed *sc-exo-* and *ap*-conformations (*cf.* [18b] and *Fig. 4*) of the exocyclic bond of the pyrrolidine ring have been optimized.

Configuration	Method	Energy [kcal/mol]		Pyramidalization Δ [Å] on N	
(*E*)/(*Z*)		(*E*)	(*Z*)	(*E*)	(*Z*)
 **10b**	*A*	0	+0.26	0.30	0.28
	C	0	+0.25	0.36	0.34
 **10c** *sc-exo*	*A*	+0.77	0	0.27	0.24
	B	+2.79	0	0.18	0.11
 **10c** *ap*	*A*	0	+1.22	0.21	0.17
	B	0	+0.95	0.02	0.03
	D	0	+0.69		
 **10d** *sc-exo*	*A*	+2.64	0	0.28	0.25
	B	+2.55	0	0.16	0.15
 **10d** *ap*	*A*	+1.90	0	0.21	0.17
	B	0	+2.17	0.00	0.05

attract one another), which resulted in a significant structural distortion of each *ap*-isomer. This distortion is facilitated by a phenyl ring that, in the *ap*-conformation, can interact with the neighboring alkoxy substituent. However, because of the empirical character of the D3 dispersion correction, this observation should not be over-interpreted. In condensed phase, these interactions are likely to be reduced because of

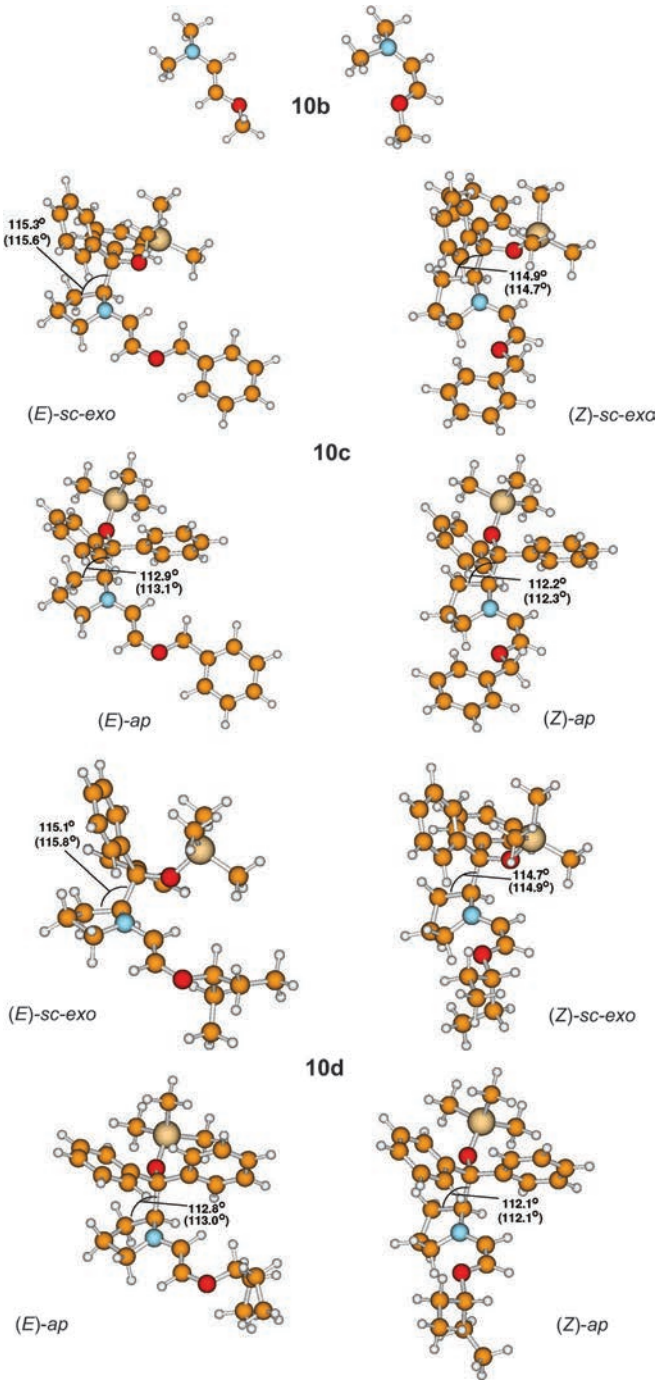


Fig. 8. *BP86/TZVPP Structures of the* (E)*- and* (Z)*-alkoxy enamines* **10b**, **10c**, *and* **10d** *with the 'exocyclic' bond angles C(3)–C(2)–C(substituent)*. The angles in parentheses are those obtained with BP86-D3/TZVPP.

additional interactions that become possible with solvent molecules. Still, it clearly demonstrates that dispersion interactions of the bulky substituents can be more pronounced in the *ap*-conformer when compared to the *sc-exo* conformer.

In conclusion, the N-pyramidalization of enamines, found in X-ray crystal structures and discussed by *Eschenmoser*, *Dunitz*, and our groups [18b][25h–l], was confirmed by the calculations. The direction of the pyramidalization was such that electrophilic attack from the face anti to the large substituent in **10a** would also be stereoelectronically favored.

Another interesting observation is evident from an inspection of the '*exocyclic*' *bond angles* in *Fig. 8:* in all cases, the (diphenyl)(trimethylsilyloxy)methyl group is in a *quasi*-axial position on the puckered pyrrolidine ring, with a C(3)–C(2)–C(*exo*) bond angle, which is substantially larger than the tetrahedral angle of 109°, *i.e.* 114.7–115.8° in the *sc*-conformations and 112.1–113.1° in the *ap*-conformations of **10c** and **10d**. This leads to a closer proximity of the large substituent with the enamino double bond (increasing steric shielding for attack of an electrophile from the *cis*-face of the double bond?).

We next discuss the *relative energies of (*Z*)- and (*E*)-alkoxy-enamines* **10** (see *Table 2*). When we compared the electronic energies of the generic Me-substituted compounds **10b**, for which MP2 calculations with a sufficiently large basis set are feasible, we found a rather small difference of 0.26 (BP86/TZVPP) and 0.25 kcal/mol (MP2/def2-QZVPP), respectively, with the (*E*)-isomer being more stable than the (*Z*)-isomer. Importantly, the BP86 result deviated only by 0.01 kcal/mol from the MP2 energy difference, which is an indication that the BP86 functional can be taken as a sufficiently accurate model for the description of the large derivatives.

However, two effects make the energetic comparison of the large derivatives more complicated. One is that dispersion interactions can play a significant role because of the bulky substituents. The other one is the multitude of stable conformers, which is difficult to sample in a standard quantum-chemical approach. While we have already considered the first issue above, we need to discuss the latter one in more detail, especially for the isopentyl derivative **10d**. All structure optimizations have been carried out starting from corresponding (*E*)- and (*Z*)-isomeric structures with the same conformation with respect to the isopentyl group. This procedure does hardly introduce an energetic bias owing to the conformations of the isopentyl group, although it might slightly affect the overall energy because of different long-range intramolecular interactions. Only a rigorous sampling approach would allow us to identify the lowest-energy structures of each conformer, which is beyond the scope of the present work. Still, we can extract all relevant information from the calculations carried out for the selected conformers under study. For example, in *Fig. 8* one can clearly see that the isopentyl conformation is different for the *ap*- and *sc-exo*-isomers. To investigate the relevance of these different conformations, we also considered an isopentyl conformation for the *ap*-conformers that resembles the one of the *sc-exo* conformers. The energy of the isomers was then reduced by *ca.* 2.4 kcal/mol so that all relative energies of corresponding (*E*)- and (*Z*)-isomers and especially their energetical ordering remain essentially the same. Hence, we use the energies of the structures depicted in *Fig. 8* in the following discussion, keeping in mind that lower-energy structures might be obtained in a rigorous sampling approach.

The relative electronic energies are collected in *Table 2*. Only for the *ap*-conformers, we found the same energetic ordering of (*E*)- and (*Z*)-isomers as for the Me-substituted generic structure **10b** (*vide supra*). For the *ap*-conformer of the benzyl derivative we found that the (*Z*)-isomer is higher in energy than the (*E*)-isomer by +1.22 kcal/mol (+0.95 kcal/mol). Here and in the following paragraph, the energy difference given first was obtained with BP86/TZVPP, while the number in parenthesis is the BP86-D3/TZVPP result. Surprisingly, the *ap*-(*Z*)-conformer of the isopentyl derivative **10d** was lower in energy by −1.90 kcal/mol (+2.17 kcal/mol), while the inclusion of dispersion interactions in the structure optimization reversed this order. For the *sc-exo*-isomers, the picture is without such ambiguity. The (*Z*)-isomers of **10c** and **10d** were lower in energy. For the benzyl derivative **10c**, we found the (*Z*)-isomer to be −0.77 kcal/mol (−2.79 kcal/mol) lower in energy than the (*E*)-isomer, while it was −2.64 kcal/mol (−2.55 kcal/mol) for the isopentyl derivative **10d**.

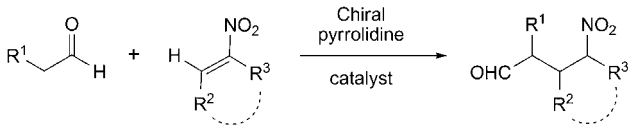
In general, we found a comparatively small energetic effect of dispersion interactions on the relative energies of (*E*)- and (*Z*)-isomers (with the sole exception of the isopentyl *ap*-structure), which can be taken as an indication that the dispersive attraction of the bulky substituents in both isomers is about the same, and hence does not affect their energy difference.

It is noteworthy that we found the *ap*-(*E*)-conformers to be lower in energy than the *sc-exo*-(*E*)-conformers of **10c** and **10d**, although the latter was usually found in X-ray structures. For the isopentyl (*E*)-isomers, *ap*-conformer was lower in energy by 0.56 kcal/mol (BP86/TZVPP) than *sc-exo*-conformer, while the difference was even larger in the case of the benzyl derivative, *i.e.*, by 3.04 kcal/mol (BP86/TZVPP).

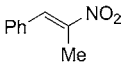
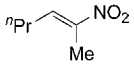
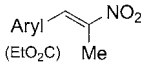
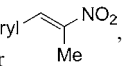
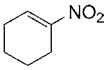
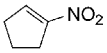
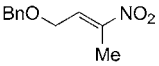
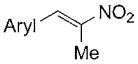
The *general conclusion* from these calculations is that the energy differences between (*E*)- and (*Z*)-isomers of the isopentyloxy-diphenylprolinol-silyl ether derivative **10d** are quite larger (1.9–2.6 kcal/mol) than experimentally observed (*ca.* 1:1; remember that a 10:1 ratio corresponds to an energy difference of 1.4 kcal/mol at room temperature). To understand this discrepancy, two explanations can be offered. First of all, the accuracy of DFT could be limited, and a more accurate wave-function-based calculation is desirable. To investigate this issue, we are currently optimizing the structures with MP2/def2-QZVPP. Moreover, the bulky substituents will interact with solvent molecules in condensed phase, and this poses a rather complicated problem, in which the molecule's solvent environment and its conformations need to be rigorously sampled.

2.2. *The Dihydro-1,2-oxazine* N-*Oxides* **5**. The organocatalytic addition of aldehydes to disubstituted nitro olefins, such as 1-phenyl-2-nitroprop-1-ene (**3**, R^2 = Ph, R^3 = Me; 'methyl-nitrostyrene') or 1-nitrocyclopentene and 1-nitrocyclohexene, with the catalyst **1** or other pyrrolidine derivatives has been found to be sluggish; these reactions required a more acidic co-catalysts, $CHCl_3$ or CH_2Cl_2 instead of toluene as solvent, and long reaction times. Some typical conditions, under which this type of *Michael* addition can be carried out, are compiled in *Table 3*. Many authors considered the disubstituted nitro olefins sterically hindered or demanding substrates. This is in contrast to the results described in 1970 by *Nielsen* and *Archibald* (see ref. in [8]), who found that α-substituted nitro olefins add to cycloalkanone-derived, *i.e.*, disubstituted, enamines to form isolable 5,6-dihydro-4*H*-oxazine 1,2-

Table 3. *Reported Additions of Aldehydes to Disubstituted Nitro Olefins* **3**, *Catalyzed by Pyrrolidine Derivatives*



3

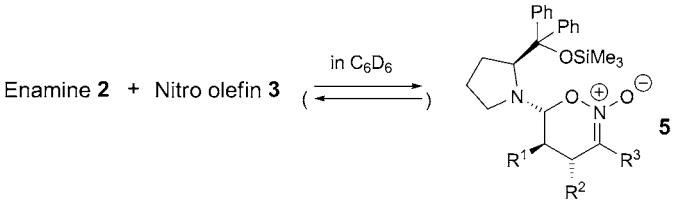
Conditions	Nitro olefin **3** Comments	Ref.
5 mol-% **1a**, 5 mol-% $4NO_2$–C_6H_4OH, toluene, r.t., up to 48 h	no reaction with  or with **3** $R^2 = {}^iPr$, $R^3 = Me$	This work
20 mol-% *ent*-**1a**, 60 mol-% $PhCO_2H$, H_2O, r.t.	no reaction with 	[27]
10 mol-% **1a**, 10 mol-% $PhCO_2H$, CH_2Cl_2, r.t., up to 48 h	reactions with 	[28]
10 mol-% **1a**, 40 mol-% 4-NO_2–C_6H_4OH, $CHCl_3$, r.t., up to 65 h	reactions with  , not with $R^1 = {}^iPr$	[12]
20 mol-% **1a**, 10 mol-% 3-NO_2–$C_6H_4CO_2H$, CH_2Cl_2, r.t., up to 54 h	reactions with 	[29a]
15 mol-% proline, Na_2SO_4, DMSO, r.t., 90 min	reaction with 	[29b]
15 mol-% pyrrolidyl-pyrrolidine, $CHCl_3$, $-10°$, 7 d	reaction with 	[30]
H-Pro-Pro-D-Gln-OH or -Asn-OH (5 mol-%), $CHCl_3$/${}^iPrOH$ 1 : 9, r.t., up to 3 d	reaction with  and nitrocyclohexene, works with $R^1 = {}^iPr$	[31]

oxides[35]) under conditions (hexane, 0–25°), which do not indicate that the reaction would be sluggish!

[35]) These authors also make the statement: '*it has been found that α-substituted nitro olefins with enamines from cycloalkanones of less than eight ring members, in polar or nonpolar aprotic solvents (hexane, MeCN, ether), lead to a zwitterion which undergoes intramolecular* O-*alkylation to a cyclic nitro ester*'. The intermediacy of a zwitterion in such reactions has been questioned by a recent calculation (see *Footnote 4* and [12]), suggesting that *oxazine* derivatives, in contrast to cyclobutanes, may be formed by a concerted (4 + 2) cycloaddition of a nitro olefin to an enamine (see also *Scheme 2*).

2.2.1. *Preparation and Identification of Oxazine Derivatives* **5**. We have now studied the stoichiometric reactions of various **1a**-derived enamines **2** ($R_3Si = Me_3Si$) with methyl-nitrostyrene (**3**, $R^2 = Ph$, $R^3 = Me$), 4-methyl-2-nitropent-2-ene (**3**, $R^2 = {}^iPr$, $R^3 = Me$), ethyl 3-nitrobut-2-enoate, and nitrocyclohexene. The reactions were carried out as with the monosubstituted nitroethenes (*cf. Scheme 4*): to the enamine solution in C_6D_6 (NMR tube, in the presence of 4-Å MS, room temperature) was added an equimolar amount of the nitro olefin, and the first spectrum was recorded within *ca.* 10 min. The results are collected in *Table 4.* In all cases, the disubstituted nitro olefins gave (4 + 2) cycloadducts **5** (see formulae in *Fig. 2* and X-ray structures in *Fig. 4*). Compounds **5** were formed upon mixing of the components (*i.e.*, **5b**, **5c**, and **5h**), except when the ${}^iPr$-substituted enamine **2** ($R^1 = {}^iPr$) was employed (**5d**, **5e**, and **5f** took hours or days for high degrees of conversions). To see whether the cycloadducts are in equilibrium with the precursors, we warmed the solutions to 50°, cooled them back down to ambient temperatures, and determined the ratios oxazine derivative **5**/corresponding enamine **2** by suitable NMR-peak integrations: equilibration could be detected with the ${}^iPr$/Ph/Me-substituted derivative **5d** and the bicyclic compound **5f** (derived from nitrocyclohexene).

Table 4. *Cycloadditions of* **1a**-*Derived Enamines* **2** *to Disubstituted Nitro Olefins* **3** *with Formation of Oxazine Derivatives* **5**



5	R^1	R^2	R^3	Yield [%]	Time	Comments	Ref. to corresp. catal. reaction
5b	Me	Ph	Me	> 90 (NMR), 72 (recryst.)	≤ 10 min	most stable of our compounds **5**; no equilibration up to 50°	[12]
5c	${}^nPr$	Ph	Me	> 90 (NMR), 63 (recryst.)	≤ 10 min	stable up to 50°; no equilibration	[28][31]
5d	${}^iPr$	Ph	Me	> 85 (NMR), 68 (recryst.)	2 h	highly moisture-sensitive equilibrium **5d**/**2** ($R^1 = {}^iPr$) 7 : 1 (r.t.), 1.5 : 1 (50°)	[31]
5e	${}^iPr$	${}^iPr$	Me	44 (after prep. TLC)	4 d	slowest reaction	–
5h	Pr	CO_2Et	Me	> 90 (NMR)	≤ 10 min	no equilibration; rearrangement to nitro enamine **6s** within 3 d	[28]
5f	${}^iPr$	$-(CH_2)_4-$		50 (NMR)	16 h	equilibrium **5f**/**2** ($R^1 = {}^iPr$) 1 : 1 (r.t.), 1 : 3 (50°)	[29a]

2.2.2. *Chemical Properties of the Oxazine Derivatives* **5**. To learn about the role, which the (4+2) cycloadducts **5** might play in catalytic reactions, in comparison with the (2+2) cycloadducts **4**, we have investigated their properties, such as thermal stability (*Table 4*), hydrolytic stability, rearrangement, and formation from open-chain precursors (*Scheme 10,a–f*). As reported previously [1] (*cf. Scheme 6*), only the six-membered-ring compound **5a**, derived from a monosubstituted nitroethene, was shown to be in equilibrium with the corresponding cyclobutane **4a** (*Scheme 10,a*). In two cases, there was reversible dissociation of the oxazine derivative (**5d** and **5f**;*b* in *Scheme 10*). Non-hydrolytic ring opening to a linear nitro enamine, **6s**, and its reversal, **6r**→**5b**, as well as hydrolyses to nitro aldehydes were observed or studied with the ethyl-ester derivative **5h** and the heterocycles **5b**/**d**, as shown in *Scheme 10,d* and *e*, respectively. A most peculiar derivative was the oxazine *N*-oxide **5d** with 5-^{i}Pr, 3-Me, and 4-Ph substitution: it was very sensitive to moisture, but could not be converted to a linear derivative (nitro enamine or aldehyde) under the conditions tested by us, rather it fell apart to the nitro olefin, aldehyde, and pyrrolidine **1a** (the catalyst molecule; see *Scheme 10,f*)[36]).

As with the cyclobutanes, there is a discrepancy between the ease, in most cases, of cycloadduct formation and the failure of the catalytic reaction also with the oxazine derivatives (*cf. Tables 3* and *4*). The successful catalysis with disubstituted nitro olefins listed in *Table 3* required stronger acidic conditions and, most remarkably, chlorinated solvents (CH_2Cl_2 and $CHCl_3$), which are known to be solvents of choice for many organic reactions involving cationic intermediates, notably iminium ions [32][37]).

Referring to the prototypical reaction of propanal with the methylated nitrostyrene (**3**; R^2=Ph, R^3=Me), the experimental results presented in *Tables 3* and *4*, and *Scheme 10* are as follows: *i*) there was no catalytic reaction under our standard conditions [14] (5 mol-% **1a**, 5 mol-% 4-nitrophenol, toluene, room temperature, 24 h); *ii*) ≥68% yield was obtained under the conditions of *Pihko* and co-workers for the catalytic reaction [12] (10 mol-% **1a**, 40 mol-% 4-nitrophenol, $CHCl_3$, room temperature, 30 h); *iii*) upon mixing the corresponding enamine **2** (R^1=Me) with the disubstituted nitro olefin in toluene at room temperature, the oxazine derivative **5b** was formed in *ca.* 5 min; *iv*) the heterocycle **5b** was stable in C_6D_6 up to at least 50°; *v*) with 10 equiv. H_2O and 10 mol-% 4-nitrophenol, this compound was stable for 24 h in benzene; *vi*) switching to CH_2Cl_2 as solvent, 10 equiv. of H_2O and the stronger acid $PhCO_2H$ (1.1 equiv.; conditions of *Ma* and co-workers for the catalytic reaction [28]) led to hydrolysis of **5b** to the nitro aldehyde with complete conversion in 24 h (*Scheme 10,e*); *vii*) deuterolysis of **5b** (4-$NO_2C_6H_4OD$, in $CDCl_3$) furnished γ-nitro aldehyde with >50% D in the α- and <10%

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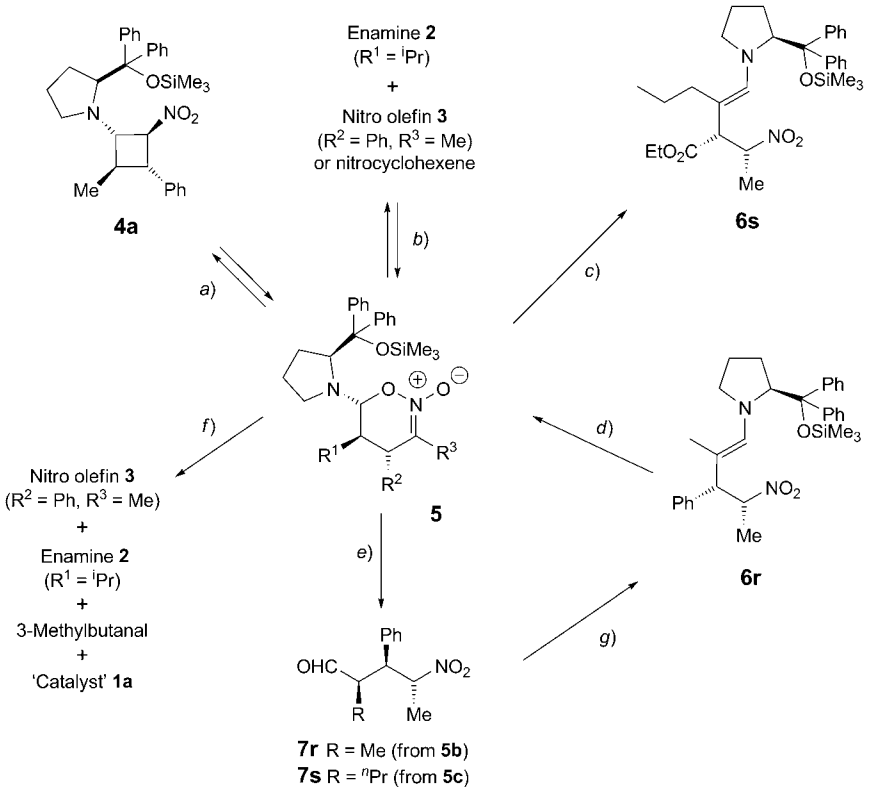
36) As far as we know, there has been only one report on an organocatalytic *Michael* addition of 3-methylbutanal to disubstituted nitro olefins (by one of our groups (*H. W.* [31])).

37) An example relevant to the discussion of this subject is the reaction of nitrostyrene with the **1a**-derived enamine **2**, R^1=Me, R_3Si=Me_3Si, to give the nitro enamine **6a**: it took *15 h* at room temperature in toluene and ≤*5 min* in CD_2Cl_2; see *Scheme 6*, and also Footnote 12 and Scheme 6 in [1].

Scheme 10. *Conversions and Formations of Oxazin* N-*Oxide Derivatives* **5**



a) Equilibrium of **5a** with **4a** (C_6D_6, room temperature; *Scheme 6*) [1][12][17]. *b*) Equilibrium of enamine and nitro olefin with **5** (see *Table 3*); for similar results with R^2 = 4-F–C_6H_4, see [12]. *c*) Ring opening of **5h** to nitro enamine **6s** (C_6D_6, 3-Å MS, room temperature, 3 days, > 99% conversion, 96% yield; dr 95 : 5) + 4% nitro aldehyde. *d*) Ring closure of nitro enamine **6r** to **5b** ((D$_8$)toluene, 40 mol-% 4-NO_2–C_6H_4OH, 3-Å MS, room temperature, 24 h; 30% conversion); for a similar experiment, see Supplementary Material in [12]. *e*) Hydrolysis of **5b** (10 equiv. H_2O, C_6D_6, room temperature, 24 h: no reaction; after addition of 10 mol-% 4-(NO_2)C_6H_4OH, r.t., 24 h: no reaction; with 10 equiv. H_2O, 1.1 equiv. $PhCO_2H$, CD_2Cl_2, room temperature, 24 h: > 98% conversion to nitro aldehyde **7r** of dr 66 : 24 : 8 : 2); hydrolysis of **5c** (10 equiv. H_2O, 1.1 equiv. $PhCO_2H$, CH_2Cl_2, room temperature, 24 h: 67% nitro aldehyde after chromatography); deuterolysis of **5b** (4 equiv. 4-NO_2–C_6H_4OD, 1.5 equiv. D_2O, $CDCl_3$, room temperature, 17 h) gives 41% γ-nitro aldehyde with > 50% D in α- and < 10% in γ-position. *f*) Products formed from moisture-sensitive **5d** in C_6D_6 at room temperature on contact with air: the oxazine derivative disassembled to its precursors; similarly, treatment of **5d** with 10 equiv. of H_2O, 1 equiv. of $PhCO_2H$, $CDCl_3$, room temperature, leads to total destruction; no nitro aldehyde detected in the product mixture. *g*) Conversion of a nitro aldehyde **7r** (R = Me) to nitro enamine **6r** (**7r**/**1a** 1 : 1; 3-Å MS, (D$_8$)toluene, room temperature, $\leq$ 10 min: > 90% conversion to **6r** of high diastereoisomeric purity); for a similar experiment with the nitro aldehyde lacking the Me group next to NO_2, see [17a].

D in the γ-position[38]); *viii*) treatment of the Me/Ph/Me-substituted nitro enamine **6r** with 4-nitrophenol (anhydrous conditions in toluene) caused cyclization to the oxazine derivative **5b** (*Scheme 10,d*; in an equilibration?).

Thus, at least in this case, it must be *concluded for the catalytic reaction* that the plethora of conditions listed in *Table 3* have, actually, not been elaborated to force the intermediate enamine to add to the disubstituted nitro olefin, but to hydrolyze the intermediate oxazine *N*-oxide derivative to the product nitro aldehyde. In general terms, the exact route of formation of the (4+2) cycloadducts **5** (zwitterion or concerted one-step reaction[4])) and of their hydrolysis to nitro aldehydes (site of protonation, direct acid-catalyzed hydrolysis[5])[38]), or zwitterion) still need to be discussed (see **D** → **F** *vs.* **D** → **G** → **F** in *Scheme 2*).

3. Intermediates 13 and 14 in Tripeptide-Catalyzed *Michael* Additions. – One of our groups (*H. W.*) reported that tripeptides of the general type H-Pro-Pro-Xaa-X (with Xaa bearing a CO_2H group; *e.g.*, **11a** in *Fig. 9*) are excellent catalysts (with loading of $\leq$1 mol-%) for enantioselective additions of aldehydes to monosubstituted nitro olefins [37][39]). Two such tripeptides have recently been found to catalyze aldehyde addition to disubstituted nitro olefins [31]; the reactions were much slower and required more catalyst (5 mol-%) than with monosubstituted nitro olefins. The important role of the intramolecularly available CO_2H group was demonstrated by employing corresponding methyl esters, which were much less active [19][37d]. Thus, trapping of short-lived species, such as zwitterions, or a kind of intramolecular acid-catalyzed hydrolysis of intermediates, such as cyclobutanes or oxazine derivatives, was proposed to explain the catalytic activity of these peptidic carboxylic acids.

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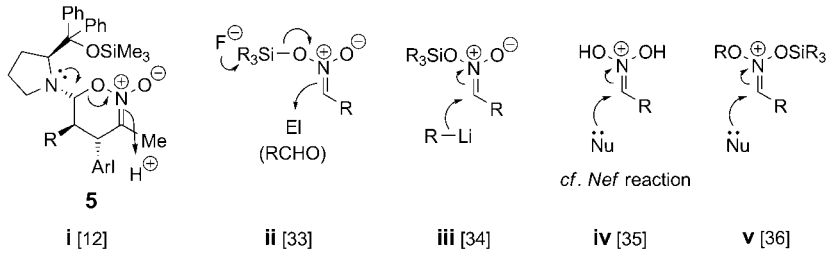
38) *Pihko* and co-workers have recently proposed [12], based on DFT calculations, that the heterocycle **5** was protonated at C(3) stereoselectively, as indicated in **i** (*cf.* **D** → **F** in *Scheme 2*); compounds **5** are cyclic nitronic acid esters, and, at the same time N/O-acetal derivatives. The same type of reactivity, *i.e.*, attack by electrophiles, was observed in the fluoride-catalyzed additions of silyl-nitronates to aldehydes (see **ii**). The opposite reactivity, *i.e.*, attack by nucleophiles on nitronate C-atoms, was observed with organolithium compounds (*cf.* **iii**), in the *Nef* reaction (*cf.* **iv**), and with *O*-silylated nitronate esters (*cf.* **v**), which are kind of iminium ions. The result of the deuterolysis experiment (*Scheme 10,e*) is not compatible with protonation at C(3) of **5b**.



i [12] **ii** [33] **iii** [34] **iv** [35] **v** [36]

39) Simple oligoprolines have also been tested for, *e.g.*, H-$(Pro)_{2,3,4}$-OH, H-$(Pro)_3$-OBn, H-$(Pro)_3$NHBn, and H-(β^3h-Pro)$_2$-OH. They are quite active catalysts (short reaction time, good-to-excellent diastereoselectivity), but the enantioselectivities, determined in some selected examples, were poor: hitherto unpublished results (*N. P.*, ETH Zürich, 2012) and Universität Basel, 2009 [38].

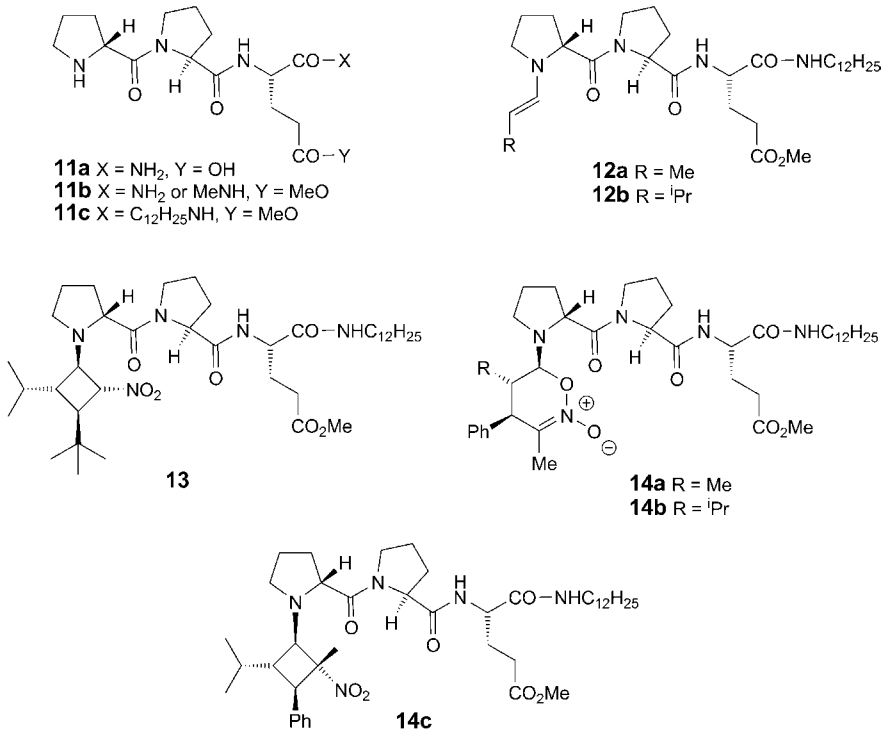


Fig. 9. *Tripeptide derivatives* **11**, *used as organocatalysts for* Michael *additions to mono- and disubstituted nitro olefins* [19][31][37][38], *and/or identified or isolated enamines, as well as (2+2) and (4+2) adducts* **12**–**14**, *formed with* **11c**. The configuration of the cyclobutane stereogenic center carrying NO_2 and Me in **14c** could not be safely deduced from the NMR spectra; it is tentatively assigned as (*R*), as expected from the collapse of the corresponding zwitterion. The amido-carboxylic acid derivatives of type **11a** and analogs containing Asp or Asn residues, as well as epimers with reversed configuration of one of the residues were also used or tested as catalysts. For disubstituted nitro olefins, H-Pro-Pro-D-Gln-OH and H-Pro-Pro-Asn-OH turned out to give best results in catalytic reactions [31].

We have now looked for stable intermediates in stoichiometric reactions. To prevent the action of CO_2H groups and to have better solubility in organic solvents, we used compounds **11b** and **11c** with a methyl ester group in the side chain and a terminal *N*-dodecylcarbamoyl group [19][37g][40]) (*Fig. 9*). As aldehyde components, we chose propanal and 3-methylbutanal, from which the enamines **12** formed immediately with **11c** under our standard conditions (C_6D_6, 4-Å MS, room temperature). The solution of the ^{i}Pr-substituted enamine **12b** was combined with 4,4-dimethyl-1-nitrobut-1-ene, *i.e.*, the ^{t}Bu-substituted nitroethene, which had led to the most stable cyclobutane, **4q**, with the **1a**-derived enamine. The corresponding cyclobutane **13** was indeed formed

[40]) Experiments with **11b**, which would have been better candidates for crystallizations of intermediates, were not successful.

(reaction time at room temperature, 20 h) and could be isolated in 52% yield after preparative TLC. In search for oxazine derivatives, we first chose enamine **12a** and 2-nitro-1-phenylpropene; product **14a** was formed with complete conversion within $\leq$ 10 min; while the prolinol-derived analog **5b** was the most stable (4 + 2) cycloadduct (**5b**; *Scheme 10,e*), **14a** decomposed during attempts to crystallize it. The adduct **14b** with an ^{i}Pr group at C(5) of the heterocycle was formed much more slowly (2 h) and had the same peculiar properties as the **1a**-derived analog **5d** (*cf. Scheme 10,f*): it is in equilibrium with its precursors (**12b**/**14b** 1 : 7 at room temperature and 1 : 1.5 at 50°), and it falls apart to its components **11c**, aldehyde, and nitro olefin upon contact with moisture (without and with added $PhCO_2H$).

In the NMR spectrum of the reaction mixture obtained from the enamine **12b** and the disubstituted nitro olefin, we detected signals not only of the oxazine derivative **14b** (in equilibrium with the reactants) but also of an isomeric compound, likewise in equilibrium with **14b** (EXSY measurement). To our surprise, this isomer turned out to be the cyclobutane derivative **14c** (*Fig. 9*), which was identified on the basis of characteristic NMR signals and NOEs (*cf.* compounds **4** and *Exper. Part*). The cyclobutane **14c** was actually the main product: **14c**/**14b** at room temperature 1.5 : 1. Thus, the experiments with the tripeptide ester/amide **11c** have provided the first example of (2 + 2)-adduct formation with a *di*substituted nitro olefin. As with the products from the monosubstituted nitro olefin (*cf. Scheme 6* and *Fig. 5*), there was an equilibrium between starting materials (nitro olefin + enamine **12b**), four-membered ring (**14c**), and six-membered ring (**14b**). No signal characteristic of a nitro enamine was detected in these experiments.

The power of the intramolecular CO_2H group in catalyses with tripeptides Pro-Pro-D-Gln-OH and H-Pro-Pro-Asn-OH (epimers or lower homologs of **11a**) becomes evident by the fact that this is the only method, so far, by which 3-methylbutanal[41]) has been added to 2-nitro-1-phenylprop-1-ene, to give 2-isopropyl-4-nitro-3-phenylpentanal[42])[43]). There may be a 'connection' between this successful catalytic reaction and the detection of a (2 + 2) cycloadduct with the 3-methylbutanal-derived enamine **12b**.

Thus, the same resting states/intermediates are formed when tripeptidic catalysts lacking a suitably positioned proton donor are used as those in the catalysis by the pyrrolidines **1** [19]. At which stage of the catalytic cycle the intramolecular CO_2H group of the peptidic catalyst plays a major role can, of course, not be deduced from our stoichiometric experiments. For reactions of monosubstituted nitro olefins, it is known that both, the cyclobutane (resting state) formation and ring opening, are acid-catalyzed [14]. In reactions of disubstituted nitro olefins, the oxazine *N*-oxides formed (as resting states or in-cycle intermediates) also require acid for the hydrolysis to the

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41) In only two publications cited in *Tables 3* and *4* did we find an example, in which this, otherwise common, β-branched aldehyde has been added to a disubstituted nitro olefin. Exception 1: catalysis with the tripeptide [31]; exception 2: addition to nitrocyclohexene [29a].

42) Of course, we cannot be sure whether the authors of one of the other reports actually tried – it is no more customary to mention unsuccessful experiments, *i.e.*, to give the *limitations* of a method [39].

43) The configuration of the NO_2-substituted stereogenic center is set in the protonation step from the (*Si*) diastereotopic face of an open-chain nitronate anion moiety (of a zwitterion?) [31][40][41] or of C(3) of an oxazine derivative (see **i**) in *Footnote 38* [12]).

desired open-chain nitro aldehydes. As an attractive common intermediate for all these reactions the elusive zwitterion (*cf.* **G** in *Scheme 2*) cannot be excluded, which would be efficiently trapped by the internal CO_2H group of the tripeptide acids ('how to hit a moving target') [19][31][37].

4. Addition of Aldehydes to Nitro Olefins Carrying an OH Group. – The ultimate 'catch' of a zwitterion may occur when the nitro olefin contains a nucleophilic substituent, so that, after coupling of the trigonal centers (*cf.* **K** in *Fig. 10*), there is intramolecular addition to the iminium end of the zwitterion (*cf.* **L** or **M** in *Fig. 10*). In fact, the 2-nitro-3-phenylprop-2-en-1-ol (**15**), the (benzyloxy)carbonyl (Cbz) analog **17**

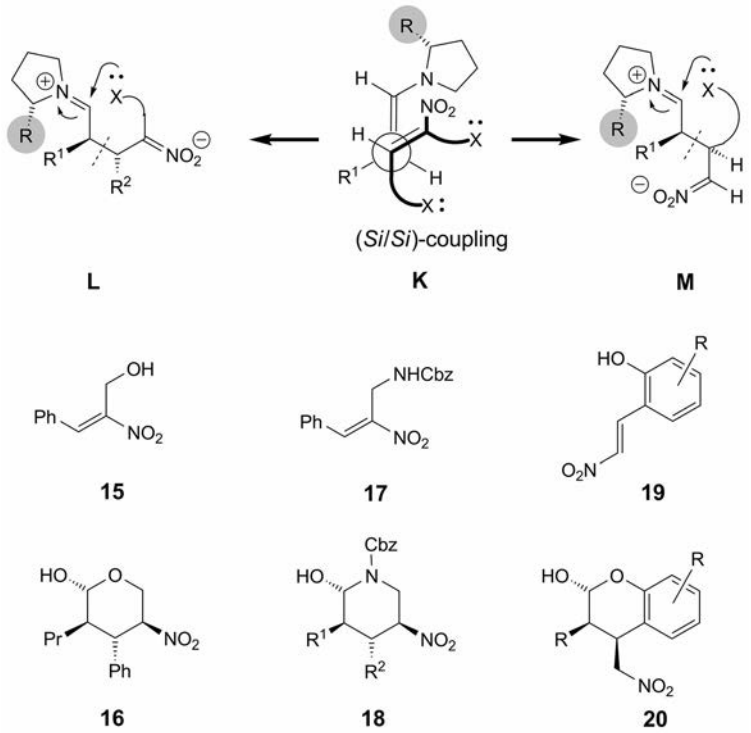
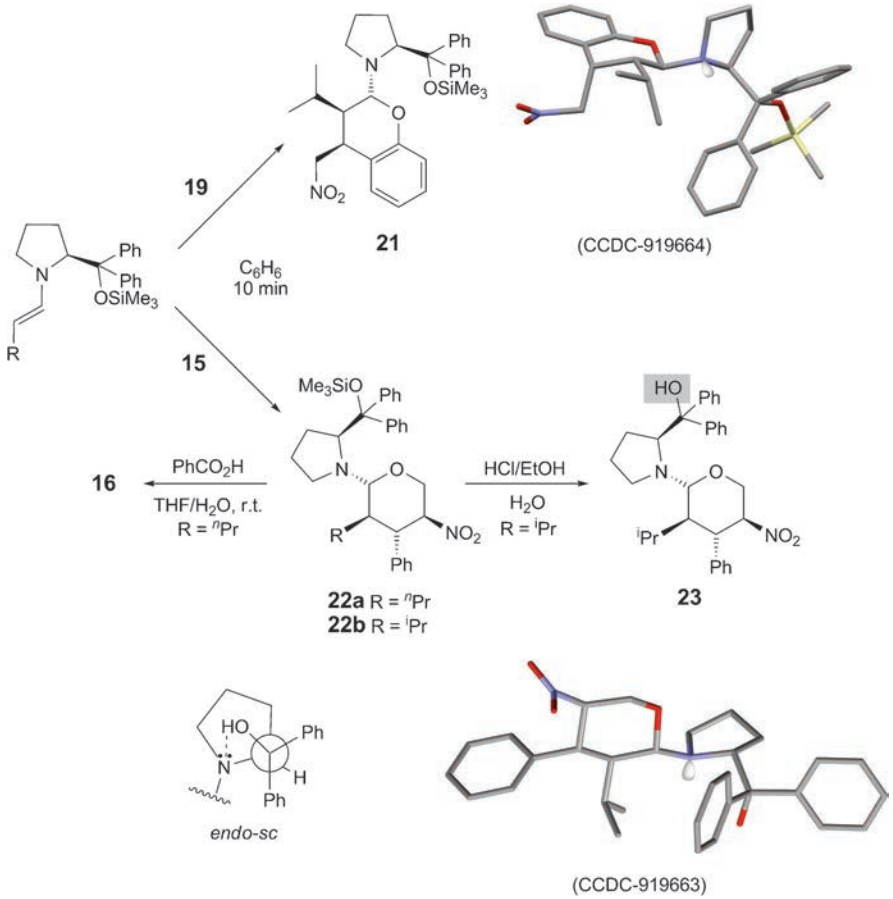


Fig. 10. *Tetrahydropyrane and piperidine derivatives,* **16** *and* **20**, *and* **18**, *respectively, are formed in* **1a**-*catalyzed additions of aldehydes to nitro olefins,* i.e., **15**, **17**, *and* **19**, *carrying nucleophilic substituents* [27][42][43]. The observed product configurations can be derived from the trajectory **K**. Intramolecular trapping, *i.e.*, **L** and **M**, of an intermediate zwitterion may be involved. Conditions: for **15** → **16**: 1 equiv. **15**, 2 equiv. aldehyde, 20 mol-% *ent*-**1a**, 60 mol-% $PhCO_2H$, H_2O, room temperature); for **17** → **18**: 1 equiv. **17**, 2 equiv. aldehyde, 10 mol-% *ent*-**1a**, 30 mol-% $PhCO_2H$, H_2O, room temperature; **19** → **20** (1 equiv. **19**, 3 equiv. aldehyde, 15 mol-% **1a**, 25 equiv. AcOH, r.t., 12–72 h) [27][42][43]. The compounds **15** and **17** are proposed to have a structure with intramolecular six-membered-ring H-bond (in H_2O, *cf. Table 1*), and thus be 'activated' [27]. Note that, in our experiments with **15** and **17**, the pyrrolidine **1a** was used (see *Scheme 11*), while *Ma* and co-workers [27] employed *ent*-**1a** in the reported catalytic reaction. For simplicity, we use the formulae of the (*S*)-prolinol-derived compounds and intermediates herein and in *Scheme 11*.

Scheme 11. *Possible Intermediates,* **21** *and* **22***, in the* **1b**-*Catalyzed* Michael *Additions of Pentanal and 3-Methylbutanal to OH-Substituted Nitro Olefins* **15** *and* **19** (see *Fig. 10*)*, and Crystal Structures of* **21** *and* **23**. While the ^{n}Pr-substituted **22a** can be hydrolyzed to the product, *i.e.*, **16**, of the catalytic reaction [27], the ^{i}Pr derivative **22b** cannot; under forcing conditions, **22b** is desilylated (→**23**). For a possible reason of the discrepancy between **22a** and **22b**, see *Fig. 11* and accompanying text. Note that the conformation of the exocyclic bond on the pyrrolidine ring in **23** is *endo-synclinal* (O–C–C–N dihedral angle *ca.* −60°). This type of conformation has not been observed before (*cf. Fig. 4* and [18b]) in structures of diphenylprolinol derivatives; it is due to a H-bond between the OH group and the N-atom in **23**.



(or NHAc and NHBoc derivatives) and *ortho*-hydroxy-nitrostyrenes **19** react with aldehydes, catalyzed by pyrrolidine **1a**, to give heterocyclic products **16**, **18**, and **20**, respectively (*Fig. 10*) [27] [42] [43][44]). Both groups, which have published these results,

[44]) Similar reactions involving dienamine intermediates [44] or ketone-derived intermediates [45], and various co-catalysts have been reported. For dienamine intermediates adding to nitrostyrenes, see also [46].

assumed that the cyclic hemiacetal/aminal derivatives, **16**, **18**, and **20**, were actually formed by cyclization of the corresponding OH- and carbamoyl-substituted aldehydes, respectively, rather than by cyclization of a zwitterion (*cf.* **L** and **M**). To test this latter possible mode of reaction, we have, once more, carried out stoichiometric reactions (*Scheme 11*): to the (D_6)benzene solutions of the **1a**-derived enamines of pentanal or of 3-methylbutanal were added the hydroxy-nitro olefins **15** and **19** (R = H). In all cases there was instantaneous formation of the cyclic aminals **21** and **22**, respectively, which turned out to be stable enough to be isolated and purified (single diastereoisomers **22a** and **22b** in 77 and 66% yield, respectively, *Scheme 11*). With these two products, obtained with the $HOCH_2$-substituted nitrostyrene **15**, we performed hydrolysis experiments under conditions similar to those used in the reported catalytic reaction ($PhCO_2H$, H_2O). The ^{n}Pr-substituted heterocycle **22a** underwent replacement of the pyrrolidin-1-yl by a OH group, *i.e.*, the product **16** of the catalytic reaction was isolated. In contrast, the ^{i}Pr-substituted **22b** was stable under these conditions. After testing various other hydrolysis conditions, we found that a reaction with a 1:1 mixture HCl (10%)/EtOH occurred, which did, however, not lead to the cyclic hemiacetal but produced the OH compound **23**, *i.e.*, the product of desilylation (!), of which an X-ray structure was obtained (*Scheme 11*). No wonder, was there no catalytic reaction reported [27][45]) or possible in our laboratory (*X. S.*) with 3-methylbutanal and nitro olefin **15**: the amino THP derivative **22**, R = ^{i}Pr, is an irreversible trap, for the catalyst **1a**.

The stunning difference between the ^{n}Pr and the ^{i}Pr derivatives **22a** and **22b**, respectively, may be attributed to two fundamental steric effects: stereoelectronic interaction [18a] and 1,5-repulsion[46]). Inspection of the crystal structure of **23** (*Scheme 11*) shows that all four substituents on the THP ring are equatorial in a chair conformation of the six-membered ring (**N** in *Fig. 11*)[47]). For a stereoelectronically assisted, S_N1-type replacement of the pyrrolidin-1-yl by an OH group at the anomeric center of the THP ring, the leaving group has to be antiperiplanar (*ap*) to an electron pair at the O-atom [18a], to form an intermediate oxenium ion. This would require a ring inversion to an 'impossible', all-axially substituted chair conformation (*cf.* **O** in *Fig. 11*). A conformation, in which the stereoelectronic requirement is met, would be the boat form **P** with quasi-equatorial disposition of an ^{n}Pr group at C(3); replacement of the ^{n}Pr by ^{i}Pr in this position will generate 1,5-repulsion either between Me and O, or between Me and the benzene ring; this destabilizing effect (**Q** in *Fig. 11*) might be the reason why the ^{i}Pr group actually prevents hydrolysis of **22b** to the hemiacetal **16** (^{i}Pr instead of ^{n}Pr), or slows it down to an extent that desilylation becomes the faster process. In the case of the piperidine derivatives **18**, R^1 = ^{i}Pr, and of the chromanes **20**

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45) *Cf. Footnote 42.*

46) The generic term 1.5-repulsion or *Newman* strain [47] includes the 1,3-diaxial effect in cyclohexane chair conformations, the double *gauche*-pentane effect, the $A^{1,3}$ effect on double bonds, the *ortho*/*ortho'*-effect in biaryls, the *peri*-repulsion in 1,8-position of naphthalene, *etc.*

47) Comparison of the NMR spectra of **22b** and **23** leaves no doubt that the six-membered rings have the same conformation in both compounds.

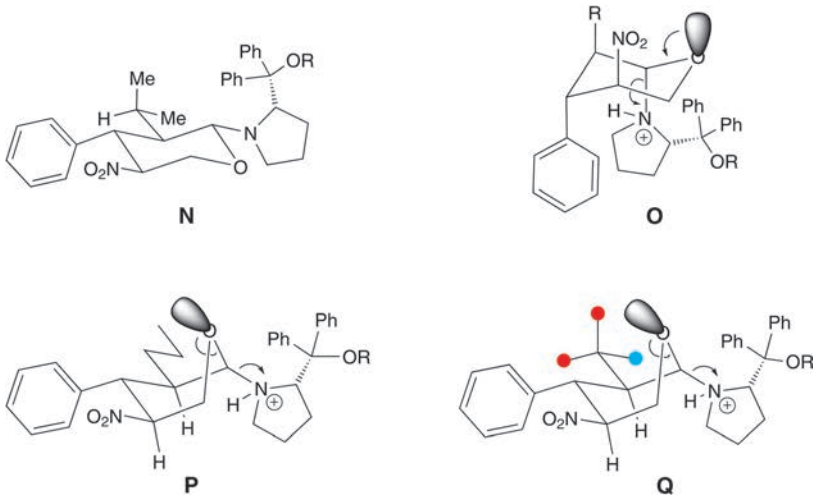
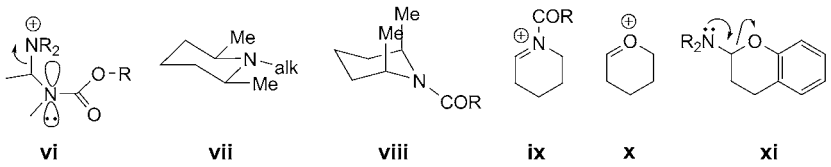


Fig. 11. *Conformational analyses of the tetrahydropyran* (THP) *derivatives* **22** *and* **23**. All-equatorially substituted conformation **N** (*cf.* X-ray structure of **23** in *Scheme 11*). Sterically 'impossible' all-axial conformation **O**. Boat conformation **P** of **22a**, from which lone-pair-assisted elimination of the R_2NH group could take place. Replacement of ^{n}Pr by ^{i}Pr in **P** leads to **Q**, of which all three conformations (● (blue) = Me, ●/● (red) = Me/H or H/Me) around the exocyclic C–C bond are subject to 1,5-repulsion (Me/O or Me/Ph).

(see *Fig. 10* and *Scheme 11*), the ^{i}Pr group does apparently not prevent release of the catalyst [27][42][43][48]).

5. Conclusions. – *In situ* NMR Investigations and isolations of products from 1:1 conversions of (diphenyl-silyloxy-methyl)-pyrrolidino enamines with nitro olefins have been used to study the chemical properties of intermediates in the catalytic *Michael* addition of aldehydes to mono- and disubstituted nitroethens. Some of the primary adducts (cyclobutane, oxazine, and THP derivatives) are thermally and/or hydrolytically so stable that they become traps for the catalyst moiety, and thus prevent successful catalysis. For alkoxy aldehydes, nitroacrylates, and acetamido-nitroethene,

[48]) The conformations of the corresponding intermediates are different: in *N*-acyl-piperidines, the $A^{1,3}$ strain pushes 2,6-substituents (*cf.* the pyrrolidino groups) into axial positions ('out' of the amide plane), see **vi**, the X-ray structures of **vii** and **viii** (CCDC: SUZBIY and BZOPIP), and the discussion in [48]; furthermore, an acyliminium ion, **ix**, is more stable than an oxenium ion, **x** [49]. Chromanes have a more flexible, cyclohexene-type conformation as compared to THPs, and the O-atom in a chromane is a better (phenolic) leaving group, so that ring opening to an iminium ion, **xi**, and hydrolysis thereof is more likely to occur.



components of the key steps in oseltamivir syntheses, a new possible resting state of the catalyst (its adduct to the acrylate) and *cis*/*trans*-equilibrations of the intermediate enamine and of the nitro olefin have been identified as complicating factors for establishing a catalytic cycle. Computational investigations show larger energy differences between (*Z*)- and (*E*)-alkoxy enamines than experimentally observed. With an ester of the H-D-Pro-Pro-Glu-tripeptide-derived organocatalyst we have shown that the same type of intermediates, *i.e.*, (2 + 2) and (4 + 2) cycloadducts, are involved as with the prolinol-derived catalysts; a unique cyclobutane derived from a disubstituted nitro olefin has been discovered with this peptide derivative. Results of hydrolysis and deuterolysis experiments with a product nitro enamine and with a dihydro-oxazine *N*-oxide are not compatible with previously reported experimental and calculational results. The numerous published optimizations of conditions for the catalytic processes, especially with disubstituted nitroethenes, have apparently not addressed the actual *Michael* addition step (of the enamines to the nitro-olefin acceptors) but the 'recovery' of the catalyst molecule from a primary product – in most cases. This is also suggested for reactions of 2-nitro-3-phenylprop-2-en-1-ol and of a nitrostyrene carrying a phenolic *ortho*-OH group. The crystal structures of seven intermediates/catalyst traps are shown.

Our experiments[11]) with stoichiometric conversions of enamines (derived from the pyrrolidine derivatives **1** and **11c**) and nitro olefins have provided evidence for equilibria at ambient temperatures, or slightly above, between

- (*E*)- and (*Z*)-enamine (**10a**; *Schemes 3*, *9*)
- (*E*)- and (*Z*)-nitro olefin (*Scheme 3* and *Table 1*)
- nitro olefin + catalyst and an amino-nitro ester (*Scheme 8* and *Table 7*)
- enamine + nitro olefin and cyclobutanes (*Figs. 5* and *9*, and *Scheme 5*)
- enamine + nitro olefin and oxazine derivatives (*Table 4*, *Fig. 9*, and *Scheme 10*)
- cyclobutanes (*Figs. 6* and *7*)
- cyclobutanes and oxazine derivatives (*Schemes 6*, and *10*, and *Fig. 9*)
- nitro enamine and oxazine derivative (*Scheme 10*)

Thus, there are surprisingly small energy (stability) differences between the (2 + 2) and the (4 + 2) cycloadduct, but also between these cycloadducts and their reactant precursors, as well as their products, setting the stage for a flat energy landscape of interconverting species[49]).

Finally, we should like to draw five *general conclusions.*

a) *There is not a single catalytic cycle* for the various reactants of the 'simple' catalytic *Michael* addition of aldehydes to nitro olefins shown in *Scheme 1*, and we speculate that this will also be true for other types of organocatalytic reactions.

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[49]) For the three generic compounds with and without a Me group, **xii** – **xiv** and **xv** – **xvii**, respectively, in α-position to the NO_2 group, we have calculated the relative energies, using Spartan'08, PM3 for identifying reasonable conformations (*cf.* the crystal structures in *Fig. 4*), which were then subjected to a low-level DFT calculation (B3LYP/6-31G*). The energy differences between the isomers (numbers [kcal/mol] next to the formulae **xii** – **xvii**) are small and can be considered compatible with the equilibria observed experimentally. The measured ΔH value of – 15.4 kcal/mol for nitro-styrene + enamine **2** → cyclobutane **4e** also compares reasonably well with the result of the corresponding calculation (– 18 kcal/mol). The – at first sight – surprisingly low energy differences

b) Stoichiometric model reactions and identifications of possible intermediates of organocatalyses may be useful tools for identifying key steps, optimizing conditions, and elucidating the stereochemical courses of the overall reactions. However, since the conditions (concentrations, solvent(s), acid additives, reaction times, presence of molecular sieves) of the catalytic and the stoichiometric reactions are different, 'mutual' mechanistic conclusions must be drawn with due care.

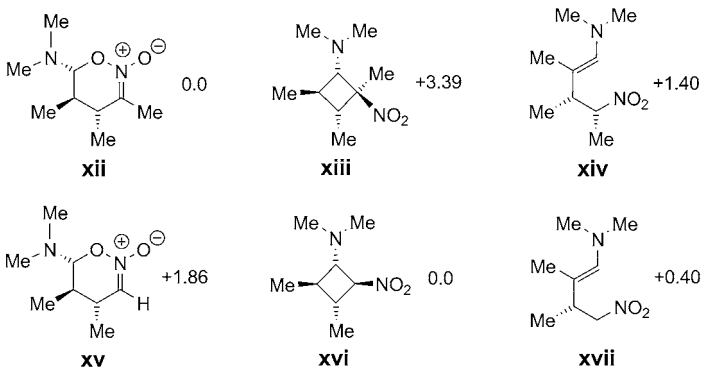
c) If an organocatalytic transformation is successful with certain reaction partners but fails with others, we recommend to carry out a traditional workup procedure and analyze for products that might be 'slow' intermediates or catalyst traps; after all, many organocatalytic transformations are carried out with 10–30 mol-% catalyst, so that substantial amounts of such catalyst derivatives may be present.

d) Thorough experimental analyses of the mechanisms of the present and of other organocatalytic conversions[50]) have all deepened our understanding, but, at the same time, increased complexity.

e) Thus, the pioneers in the field may have been right, not to look for details, but to just pragmatically optimize conditions to obtain the desired products with high yields and stereoselectivities (dr and er) to publish papers in high-impact-factor journals. After all, it is only worthwhile to study the mechanism of a synthetically valuable transformation that is of general utility.

We thank the NMR (*P. Zumbrunnen*, *R. Arnold*, and *R. Frankenstein*), the MS (*R. Häfliger*, *O. Greter*, and *L. Bertschi*), the elementary-analyses (*P. Kälin* and *M. Schneider*), and the X-ray (*M. Solar*) services of the Laboratorium für Organische Chemie (ETH Zürich) for their assistance. We also acknowledge the financial support by the *Swiss National Science Foundation* (*SNF*).

between species of type **4**, **5**, and **6** reveal that the statement made in [1]: '…*we consider this proposal unlikely from a purely intuitive chemical point of view, since […] it suggests an energetically uphill conversion of an open-chain enamino-nitronate to a cyclobutane upon protonation.*' did injustice to *Blackmond* and co-workers [17a].



[50]) For mechanistic work on *Michael* additions of aldehydes to nitro olefins, see [1][12][14][16][17][19][23b][37c]. For our contributions on the mechanisms of other organocatalytic reactions, see [18b][25k,l][50].

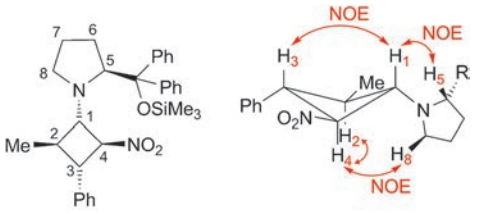
Experimental Part

General. All reactions were performed under Ar. The NMR solvents $CDCl_3$, C_6D_6, (D_8)toluene, and CD_2Cl_2 were purchased from *ARMAR Chemicals* (CH-Döttingen). Solvents for reactions and [2,2-D_2]propionaldehyde were purchased from *Sigma-Aldrich* and were used without purification and drying. The commercial aldehydes were of reagent grade and were carefully distilled prior to use. Aldehyde **9** was prepared according to [21]; its purity was 70–80%; the identity of the impurities (aldol products, trimer?) was not established; even upon storage at −78°, the amount of impurities increased slowly. Nitrostyrene (*Aldrich*), (*E*)-*β*-methyl-*β*-nitrostyrene (**3**, R^2 = Ph, R^3 = Me; *Acros*), and 1-nitrocyclohex-1-ene (*Aldrich*) are commercially available, all other nitro olefins [21][22][28][51] and the diphenylprolinol silyl ethers [52] were prepared according to literature procedures. TLC: *Merck* silica gel *60* F_{254} plates; visualization by UV fluorescence (254 mm) or by dipping into a soln. of phosphomolybdic acid (10 % in EtOH), followed by heating. FC: *Fluka* silica gel *60* (40–63 μm). M.p.: *Büchi 510* melting-point apparatus (uncorrected). Optical rotations ($[\alpha]^T_D$): *Perkin-Elmer 241* polarimeter (10 cm, 1-ml cell). IR Spectra: *Perkin-Elmer 782* spectrophotometer; $\tilde{\nu}$ in cm^{-1}. NMR spectra: *Bruker AMX 600* (^{1}H: 600 and ^{13}C: 150.9 MHz), *AMX 500* (^{1}H: 500 and ^{13}C: 125 MHz), *AMX 400* (^{1}H: 400 and ^{13}C: 100 MHz), *AM 400* (^{1}H: 400 and ^{13}C: 100 MHz), *AV-400* (^{1}H: 400 and ^{13}C: 100 MHz), or *Varian Gemini 300* (^{1}H: 300 and ^{13}C: 75 MHz); chemical shifts δ in ppm and coupling constants *J* in Hz. Peak assignments were accomplished by a combination of 1D and 2D experiments (COSY, HSQC, HMBC, and NOESY). HR-MS: *IonSpec Ultima 4.7* (HR-ESI-MS) or *Bruker* ESI-TOF-MS; *m*/*z*. Elemental analyses: performed in the Microanalytical Laboratory of the Laboratorium für Organische Chemie, ETH Zürich. Activation of molecular sieves (MS; 3 Å or 4 Å) powder by heating under reduced pressure with a heat gun, after cooling to r.t., the flask was flushed with Ar.

1. *Standard Conditions for the Catalytic* Michael *Addition of Aldehydes to Nitro Olefins* [14]. To a mixture of nitro olefin (0.3 mmol) and aldehyde (0.45 mmol) in toluene (0.3 ml) was added (*S*)-diphenylprolinol trimethylsilyl ether (=*(2*S*)-2-{diphenyl[(trimethylsilyl)oxy]methyl}pyrrolidine*; **1a**; 0.015 mmol, 5 mol-%) and 4-nitrophenol (0.015 mmol, 5 mol-%). The mixture was stirred at r.t. (monitored by TLC), and the reaction was quenched after 24 h by addition of 1M HCl, and the mixture was extracted with AcOEt (3 × 15 ml). The combined org. layer was dried ($MgSO_4$), filtered, concentrated, and analyzed for nitro aldehyde (NMR).

2. *Reactions of Enamines with Nitro Olefins. General Procedure* (*GP*). To a soln. of **1a** or **1b** (0.1 mmol) in C_6D_6 (0.6 ml, with 3- or 4-Å MS) in an NMR tube, aldehyde (0.1 mmol) was added, and the reaction was monitored by ^{1}H-NMR. After complete conversion to the enamine, nitro olefin (1.0 equiv.) was added, and the mixture was agitated at r.t., and the reaction was monitored by ^{1}H-NMR.

3. *Characterization and Properties of the Cyclobutanes* **4**. 3.1. *Characterization. (2*S*)-2-{Diphenyl-[(trimethylsilyl)oxy]methyl}-1-[(1*S*,2*R*,3*S*,4*S*)-2-methyl-4-nitro-3-phenylcyclobutyl]pyrrolidine* (**4a**) *and (4*S*,5*R*,6*R*)-6-[(2*S*)-2-{Diphenyl[(trimethylsilyl)oxy]methyl}pyrrolidin-1-yl]-5-methyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazine 2-Oxide* (**5a**). According to *GP*, from **1a** (32.6 mg, 0.1 mmol), propanal (7.2 μl, 0.1 mmol,) and *β*-nitrostyrene (14.9 mg, 0.1 mmol), **4a** and **5a** formed immediately (t < 10 min; **4a**/**5a** 4:1). FC Purification failed due to decomposition. ^{1}H-NMR of **4a**/**5a** (400 MHz, C_6D_6): Data of **4a**: 7.59–7.55 (*m*, 4 H); 7.17–7.05 (*m*, 7 H); 7.00–6.99 (*m*, 2 H); 6.87 (*t*, *J* = 7.6, 1 H); 6.70 (*d*, *J* = 7.2, 1 H); 4.99 (*t*, *J* = 8.0, 1 H); 4.43 (*dd*, *J* = 3.2, 9.6, 1 H); 4.15 (br. *s*, 1 H); 3.28 (*t*, *J* = 9.2, 1 H); 2.34–2.24 (*m*, 2 H); 1.96–1.84 (*m*, 2 H); 1.80–1.73 (*m*, 1 H); 1.23–1.15 (*m*, 1 H); 1.03 (*d*, *J* = 5.6, 3 H); 0.66–0.56 (*m*, 1 H);



4a

–0.03 (*s*, 9 H). Data of **5a**: 7.48–7.46 (*m*, 2 H); 7.42–7.37 (*m*, 2 H); 7.17–6.95 (*m*, 9 H); 6.83–6.79 (*m*, 2 H); 5.89 (*d*, *J* = 2.8, 1 H); 5.43 (br. *s*, 1 H); 4.72 (*dd*, *J* = 2.8, 9.2, 1 H); 2.95–2.89 (*m*, 2 H); 2.17–2.11 (*m*, 1 H); 1.96–1.81 (*m*, 2 H); 1.70–1.65 (*m*, 1 H); 1.42–1.29 (*m*, 1 H); 0.83 (*d*, *J* = 5.2, 3 H); 0.66–0.56 (*m*, 1 H); –0.05 (*s*, 9 H). Compounds **4a** and **5a** were identified and characterized by 1D- and 2D-NMR (COSY, HSQC, and NOESY). Equilibration between **4a** and **5a** was detected from an EXSY spectrum [1]. The data are in agreement with those in [12][16][17].

*(2*S*)-2-{Diphenyl[(trimethylsilyl)oxy]methyl}-1-[(1*S*,2*R*,3*S*,4*S*)-2-ethyl-4-nitro-3-phenylcyclobutyl]-pyrrolidine* (**4b**). Prepared according to *GP* from **1a** (32.6 mg, 0.1 mmol), butanal (8.8 µl, 0.1 mmol), and *β*-nitrostyrene (14.9 mg, 0.1 mmol). FC Purification failed due to decomposition. ^{1}H-NMR (400 MHz, C_6D_6): 7.62–6.93 (*m*, 11 H); 6.85 (*t*, *J* = 7.6, 2 H); 6.68 (*d*, *J* = 7.6, 2 H); 4.98 (*t*, *J* = 7.6, 1 H); 4.46 (*dd*, *J* = 2.8, 9.6, 1 H); 3.37 (*t*, *J* = 9.2, 1 H); 2.35 (*dd*, *J* = 4.8, 8.0, 2 H); 1.96–1.86 (*m*, 2 H); 1.84–1.74 (*m*, 2 H); 1.69–1.64 (*m*, 1 H), 1.21–1.12 (*m*, 2 H); 0.73 (*t*, *J* = 7.2, 3 H); 0.62–0.54 (*m*, 1 H); 0.02 (*s*, 9 H).

*(2*S*)-1-[(1*S*,2*R*,3*S*,4*S*)-2-Butyl-4-nitro-3-phenylcyclobutyl]-2-{diphenyl[(trimethylsilyl)oxy]methyl}-pyrrolidine* (**4c**). Prepared according to *GP* from **1a** (32.6 mg, 0.1 mmol), hexanal (12.3 µl, 0.1 mmol), and *β*-nitrostyrene (14.9 mg, 0.1 mmol). FC Purification failed due to decomposition. ^{1}H-NMR (400 MHz, C_6D_6): 7.63–7.58 (*m*, 4 H); 7.12–7.08 (*m*, 6 H); 7.05–7.03 (*m*, 4 H); 6.97–6.93 (*m*, 1 H); 5.00 (*t*, *J* = 8.0, 1 H); 4.47 (*d*, *J* = 9.2, 1 H); 3.39 (*t*, *J* = 9.2, 1 H); 2.39–2.36 (*m*, 2 H); 2.05–1.97 (*m*, 1 H); 1.84–1.77 (*m*, 1 H); 1.52–1.37 (*m*, 3 H); 1.20–1.15 (*m*, 4 H); 1.01–0.94 (*m*, 1 H); 0.87 (*t*, *J* = 6.8, 3 H); 0.78 (*q*, *J* = 6.4, 1 H); 0.62–0.51 (*m*, 1 H); –0.02 (*s*, 9 H). HR-ESI-TOF-MS: 579.3020 ($[C_{34}H_{44}N_2O_3Si + Na]^+$; calc. 579.3014).

*(2*S*)-1-{(1*S*,2*R*,3*S*,4*S*)-2-[3-(Benzyloxy)propyl]-4-nitro-3-phenylcyclobutyl}-2-{diphenyl[(trimethylsilyl)oxy]methyl}pyrrolidine* (**4d**). Prepared according to *GP* from **1a** (32.6 mg, 0.1 mmol), 5-(benzyloxy)pentanal (19.2 mg, 0.1 mmol), and *β*-nitrostyrene (14.9 mg, 0.1 mmol). FC Purification failed due to decomposition. ^{1}H-NMR (400 MHz, C_6D_6): 7.62–7.59 (*m*, 4 H); 7.55–7.49 (*m*, 2 H); 7.45–7.40 (*m*, 2 H); 7.33–7.25 (*m*, 4 H); 7.12–7.10 (*m*, 3 H); 6.97–6.94 (*m*, 2 H); 6.87–6.83 (*m*, 2 H); 6.69–6.67 (*m*, 1 H); 5.00 (*t*, *J* = 7.2, 1 H); 4.47 (*d*, *J* = 9.2, 1 H); 4.32 (*s*, 2 H); 4.31–4.24 (*m*, 1 H); 3.24–3.22 (*m*, 2 H); 2.37–2.35 (*m*, 2 H); 2.06–2.04 (*m*, 1 H); 1.89–1.76 (*m*, 4 H); 1.75–1.60 (*m*, 2 H); 1.19–1.16 (*m*, 2 H) 0.63–0.57 (*m*, 1 H); –0.02 (*s*, 9 H).

*(2*S*)-2-{Diphenyl[(trimethylsilyl)oxy]methyl}-1-[(1*S*,2*R*,3*S*,4*S*)-2-isopropyl-4-nitro-3-phenylcyclobutyl]pyrrolidine* (**4e**). Prepared according to *GP* from **1a** (32.6 mg, 0.1 mmol), isovaleraldehyde (= 3-methylbutanal; 10.8 µl, 0.1 mmol), and *β*-nitrostyrene (14.9 mg, 0.1 mmol) (*t* < 10 min). FC purification failed due to decomposition. ^{1}H-NMR (600 MHz, C_6D_6): 7.61 (*d*, *J* = 7.2, 2 H); 7.56 (*dd*, *J* = 1.8, 9.0, 2 H); 7.17–7.00 (*m*, 11 H); 4.91 (*t*, *J* = 7.8, 1 H); 4.45 (*dd*, *J* = 3.0, 9.0, 1 H); 4.24 (br. *s*, 1 H); 3.40 (*t*, *J* = 9.0, 1 H); 2.44–2.38 (*m*, 2 H); 1.91–1.78 (*m*, 3 H); 1.61–1.54 (*m*, 1 H); 1.17–1.14 (*m*, 1 H); 0.88–0.80 (*m*, 3 H); 0.60 (*d*, *J* = 6.6, 3 H); 0.54–0.46 (*m*, 1 H); –0.05 (*s*, 9 H). HR-ESI-TOF-MS: 565.2893 ($[C_{33}H_{42}N_2NaO_3Si]^+$; calc. 565.2862).

tert-*Butyl (1*R*,2*R*,3*S*,4*S*)-3-[(2*S*)-2-{Diphenyl[(trimethylsilyl)oxy]methyl}pyrrolidin-1-yl]-2-isopropyl-4-nitrocyclobutanecarboxylate* (**4g**). Prepared according to *GP* from **1a** (32.6 mg, 0.1 mmol), isovaleraldehyde (10.8 µl, 0.1 mmol), and *tert*-butyl (*E*)-3-nitroprop-2-enoate (17.3 mg, 0.1 mmol) (*t* < 10 min). FC purification failed due to decomposition. ^{1}H-NMR (300 MHz, C_6D_6): 7.59 (*d*, *J* = 6.6, 2 H); 7.54 (*d*, *J* = 7.2, 2 H); 7.16–7.06 (*m*, 6 H); 5.43 (*t*, *J* = 7.6, 1 H); 4.50 (*dd*, *J* = 3.6, 8.7, 1 H); 4.21 (br. *s*, 1 H); 3.13 (*t*, *J* = 9.0, 1 H); 2.56–2.50 (*m*, 1 H); 2.41–2.35 (*m*, 1 H); 2.00 (*q*, *J* = 8.4, 1 H); 1.83–1.75 (*m*, 2 H); 1.61–1.54 (*m*, 1 H); 1.29 (*s*, 9 H); 1.14–1.07 (*m*, 1 H); 0.88 (*d*, *J* = 6.0, 3 H); 0.77 (*d*, *J* = 6.3, 3 H); 0.56–0.43 (*m*, 1 H); –0.06 (*s*, 9 H).

*(2*S*)-2-{Diphenyl[(trimethylsilyl)oxy]methyl}-1-[(1*S*,2*S*,3*S*,4*R*)-2-nitro-3-phenyl-4-(1-phenylethyl)-cyclobutyl]pyrrolidine* (**4k**). Prepared according to *GP* from **1a** (32.6 mg, 0.1 mmol), *rac*-3-phenylbutanal (14.9 µl, 0.1 mmol), and *β*-nitrostyrene (14.9 mg, 0.1 mmol). FC Purification failed due to decomposition. The two diastereoisomers formed gave rise to the following NMR data (dr 1:1.3): ^{1}H-NMR (400 MHz, C_6D_6): Diastereoisomer A: 7.64–7.60 (*m*, 2 H); 7.52–7.48 (*m*, 2 H); 7.46–7.43 (*m*, 1 H); 7.26–7.19 (*m*, 5 H); 7.08–7.04 (*m*, 4 H); 6.96–6.92 (*m*, 4 H); 6.71–6.66 (*m*, 2 H); 5.06 (*t*, *J* = 7.2, 1 H); 4.54–4.51 (*m*, 1 H); 3.51–3.47 (*m*, 1 H); 2.73–2.66 (*m*, 2 H); 2.43–2.37 (*m*, 2 H); 2.32–2.25 (*m*, 2 H); 1.29 (*d*, *J* = 4.4, 3 H); 1.18–1.12 (*m*, 2 H); 0.59–0.49 (*m*, 1 H); 0.19 (*s*, 9 H); diastereoisomer B: 7.64–7.60 (*m*, 2 H); 7.52–7.48 (*m*, 2 H); 7.46–7.43 (*m*, 1 H); 7.26–7.19 (*m*, 5 H); 7.08–7.04 (*m*, 4 H);

6.96 – 6.92 (*m*, 4 H); 6.71 – 6.66 (*m*, 2 H); 4.89 (*t*, *J* = 7.6, 1 H); 4.41 (*d*, *J* = 8.8, 1 H); 3.44 – 3.39 (*m*, 1 H); 2.73 – 2.66 (*m*, 2 H); 2.43 – 2.37 (*m*, 2 H); 2.32 – 2.25 (*m*, 2 H); 1.03 – 0.96 (*m*, 2 H); 0.79 (*d*, *J* = 3.2, 3 H); 0.59 – 0.49 (*m*, 1 H); 0.19 (*s*, 9 H).

*(2*S*)-1-[(1*S*,2*R*,3*R*,4*S*)-2,3-Diisopropyl-4-nitrocyclobutyl]-2-{diphenyl[(trimethylsilyl)oxy]methyl}-pyrrolidine* (**4l**). Prepared according to *GP* from **1a** (32.6 mg, 0.1 mmol), isovaleraldehyde (10.8 µl, 0.1 mmol), and (*E*)-3-methyl-1-nitrobut-1-ene (11.5 mg, 0.1 mmol; *t* 17 h). FC Purification failed due to decomposition. ^{1}H-NMR (300 MHz, C_6D_6): 7.67 (*d*, *J* = 6.6, 2 H); 7.61 – 7.58 (*m*, 2 H); 7.21 – 7.08 (*m*, 6 H); 4.75 (*t*, *J* = 7.5, 1 H); 4.40 (*m*, 1 H); 4.17 (br. *s*, 1 H); 2.43 – 2.29 (*m*, 2 H); 2.22 – 2.14 (*m*, 1 H); 1.91 – 1.79 (*m*, 2 H); 1.58 – 1.12 (*m*, 4 H); 0.90 – 0.82 (*m*, 4 H); 0.74 (*d*, *J* = 6.6, 3 H); 0.66 (*dd*, *J* = 3.0, 6.9, 6 H); – 0.04 (*s*, 9 H). ^{13}C-NMR (100 MHz, C_6D_6): 144.0; 143.5; 130.6; 130.4; 80.2; 76.8; 70.4; 69.4; 68.7; 65.5; 49.8; 45.7; 45.6; 45.3; 39.6; 38.0; 31.6; 29.7; 24.3; 21.2; 20.7; 19.2; 2.5. HR-ESI-TOF-MS: 531.3024 ($[C_{30}H_{44}N_2O_3Si + Na]^+$; calc. 531.3014).

*(2*S*)-1-[(1*S*,2*R*,3*R*,4*S*)-2,3-Diisopropyl-4-nitrocyclobutyl]-2-[{[methyl(diphenyl)silyl]oxy}(diphenyl)methyl]pyrrolidine* (**4m**). Prepared according to *GP* from **1b** (45.0 mg, 0.1 mmol), isovaleraldehyde (10.8 µl, 0.1 mmol), and (*E*)-3-methyl-1-nitrobut-1-ene (11.5 mg, 0.1 mmol; *t* 16 h). FC Purification failed due to decomposition. ^{1}H-NMR (300 MHz, C_6D_6): 7.50 – 7.42 (*m*, 4 H); 7.31 – 7.09 (*m*, 14 H); 7.05 – 7.01 (*m*, 2 H); 4.70 (*t*, *J* = 7.2, 1 H); 4.13 – 4.09 (*m*, 1 H); 3.40 – 3.35 (*m*, 1 H); 2.58 – 2.52 (*m*, 2 H); 1.97 – 1.89 (*m*, 3 H); 1.61 – 1.47 (*m*, 2 H); 1.37 – 1.20 (*m*, 2 H); 1.07 (*dd*, *J* = 0.9, 6.9, 1 H); 0.75 (*dd*, *J* = 4.5, 6.6, 6 H); 0.60 (*d*, *J* = 6.6, 3 H); 0.50 (*d*, *J* = 6.6, 3 H); 0.04 (*s*, 3 H).

*(2*S*)-1-[(1*S*,2*R*,3*R*,4*S*)-3-Cyclohexyl-2-isopropyl-4-nitrocyclobutyl]-2-{diphenyl[(trimethylsilyl)oxy]-methyl}pyrrolidine* (**4n**). Prepared according to *GP* from **1a** (32.6 mg, 0.1 mmol), isovaleraldehyde (10.8 µl, 0.1 mmol), and (*E*)-(2-nitroethenyl)cyclohexane (15.5 mg, 0.1 mmol; *t* 18 h). FC Purification failed due to decomposition. ^{1}H-NMR (400 MHz, C_6D_6): 7.69 (*d*, *J* = 7.2, 2 H); 7.60 (*d*, *J* = 7.6, 2 H); 7.21 – 7.17 (*m*, 4 H); 7.13 – 7.07 (*m*, 2 H); 4.77 (*t*, *J* = 7.2, 1 H); 4.41 (*dd*, *J* = 4.0, 8.0, 1 H); 2.45 – 2.33 (*m*, 2 H); 2.22 (*q*, *J* = 8.0, 1 H); 1.96 – 1.87 (*m*, 2 H); 1.57 – 1.52 (*m*, 4 H); 1.50 – 1.48 (*m*, 3 H); 1.23 – 1.17 (*m*, 1 H); 1.12 – 1.08 (*m*, 1 H); 1.03 – 0.98 (*m*, 2 H); 0.85 – 0.80 (*m*, 2 H); 0.78 (*d*, *J* = 6.4, 6 H); 0.73 – 0.70 (*m*, 2 H); 0.54 – 0.42 (*m*, 1 H); – 0.03 (*s*, 9 H). ^{13}C-NMR (100 MHz, C_6D_6): 144.0; 143.5; 130.6; 130.5; 128.0; 127.8; 80.7; 69.4; 65.4; 49.8; 45.2; 44.2; 41.7; 31.5; 30.0; 29.8; 26.8; 26.7, 26.6; 24.3; 21.3; 19.5; 2.5. HR-ESI-TOF-MS: 571.3314 ($[C_{33}H_{48}N_2O_4Si + Na]^+$; calc. 571.3327).

*(2*S*)-1-[(1*S*,2*R*,3*R*,4*S*)-3-Cyclohexyl-2-isopropyl-4-nitrocyclobutyl]-2-[{[methyl(diphenyl)silyl]oxy}-(diphenyl)methyl]pyrrolidine* (**4o**). Prepared according to *GP* from **1b** (45.0 mg, 0.1 mmol), isovaleraldehyde (10.8 µl, 0.1 mmol), and (*E*)-(2-nitroethenyl)cyclohexane (15.5 mg, 0.1 mmol; *t* 24 h). FC Purification failed due to decomposition. ^{1}H-NMR (300 MHz, C_6D_6): 7.79 (br. *s*, 2 H); 7.65 – 7.60 (*m*, 2 H); 7.54 – 7.48 (*m*, 2 H); 7.41 – 7.38 (*m*, 2 H); 7.22 – 7.06 (*m*, 10 H); 7.01 – 6.96 (*m*, 2 H); 4.68 (*t*, *J* = 7.5, 1 H); 4.50 (*dd*, *J* = 2.1, 8.7, 1 H); 3.71 (br. *s*, 1 H); 2.49 – 2.35 (*m*, 2 H); 2.07 – 2.01 (*m*, 3 H); 1.50 – 1.37 (*m*, 5 H); 1.27 – 1.21 (*m*, 2 H); 1.01 – 0.84 (*m*, 5 H); 0.66 – 0.55 (*m*, 9 H); 0.21 (*s*, 3 H).

*(2*S*)-1-[(1*S*,2*R*,3*S*,4*S*)-3-(*tert*-Butyl)-2-ethyl-4-nitrocyclobutyl]-2-{diphenyl[(trimethylsilyl)oxy]methyl}pyrrolidine* (**4p**). Prepared according to *GP* from **1a** (32.6 mg, 0.1 mmol), butanal (8.8 µl, 0.1 mmol), and (*E*)-3,3-dimethyl-1-nitrobut-1-ene (12.9 mg, 0.1 mmol; *t* 27 h). ^{1}H-NMR (600 MHz, C_6D_6): 7.61 (*d*, *J* = 5.4, 2 H); 7.57 (*d*, *J* = 7.8, 2 H); 7.19 – 7.08 (*m*, 6 H); 4.91 (*t*, *J* = 7.8, 1 H); 4.35 (*dd*, *J* = 2.4, 9.6, 1 H); 4.08 (br. *s*, 1 H); 2.42 – 2.39 (*m*, 2 H); 2.17 (*t*, *J* = 9.0, 1 H); 1.92 – 1.74 (*m*, 2 H); 1.62 – 1.58 (*m*, 1 H); 1.51 – 1.42 (*m*, 1 H); 1.32 – 1.22 (*m*, 1 H); 1.19 – 1.17 (*m*, 1 H); 0.84 – 0.79 (*m*, 3 H); 0.65 (*s*, 9 H); 0.52 – 0.46 (*m*, 1 H); – 0.05 (*s*, 9 H).

3.2. *Thermal Equilibration between* **4e**, *and Its Precursors Enamine* **2** ($R^1 = {}^i$Pr, $R_3Si = Me_3Si$) *and β-Nitrostyrene.* In an NMR tube, **1a** (48.83 mg, 0.15 mmol) and C_6D_6 (0.70 ml) were mixed; the concentration of **1a** was 0.214M. To this soln., isovaleraldehyde (16 µl, 0.15 mmol) and MS (4 Å) were added, the mixture was agitated, and its composition was monitored by ^{1}H-NMR. According to the recorded spectra, isovaleraldehyde had been completely converted to the enamine within 10 min, and only a trace of **1a** was detected. Then, *β*-nitrostyrene (23 mg, 0.15 mmol) was added to the soln. The mixture was agitated at r.t., and a ^{1}H-NMR spectrum was recorded immediately. By ^{1}H-NMR, immediate formation of the cyclobutane **4e** was detected, but there was still some enamine **2**, *β*-nitrostyrene, and **1a** present. The ratio of these components was determined by the NMR integrals. Based on the ratio and standard concentration $[\mathbf{1a}]_0 = 0.214$M, the equilibrium concentrations of enamine **2**, *β*-nitrostyrene, and

cyclobutane **4e** at r.t. (25°) were determined: [enamine **2**] = 0.004M, [β-nitrostyrene] = 0.037M, [cyclobutane **4e**] = 0.185M. ^{1}H-NMR Spectra were recorded starting at 25°, heating up to 66°, followed by cooling back down to 25°. At various temp., the equilibrium concentrations of enamine **2**, β-nitrostyrene, and cyclobutane **4e** were determined (*Fig. 5*). From the equilibrium concentrations, the equilibrium constants (K = ([enamine] · [β-nitrostyrene])/[cyclobutane]), and the ln K values were calculated (see *Table 5*). By linear regression in *Excel*, the graph of ln K *vs.* 1/T was obtained; the data are presented in *Table 5* and *Fig. 5*.

Table 5. *Temperature-Dependent ln* K *Values for the Equilibrium between* **4e**, *and the Corresponding Enamine* **2** *and Nitrostyrene* (see *Fig. 5*)

Entry	Temperature [K]	ln K
1	298.15	– 7.1308
2	302.25	– 6.6879
3	307.95	– 6.2891
4	313.05	– 5.9304
5	318.05	– 5.6268
6	322.95	– 5.1337
7	328.15	– 4.9019
8	333.35	– 4.5461
9	339.15	– 4.1699
10	333.35	– 4.5626
11	322.95	– 5.3100
12	313.05	– 5.8850
13	298.15	– 7.7822

3.3. *Preparation of Cyclobutane* **4q** *and Investigations of Its Chemical Properties. (2*S*)-1-[(1*S*,2*R*,3*S*,4*S*)-3-(*tert*-Butyl)-2-isopropyl-4-nitrocyclobutyl]-2-{diphenyl[(trimethylsilyl)oxy]methyl}pyrrolidine* (**4q**). To a soln. of **1a** (97.5mg, 0.3 mmol) in benzene (0.3 ml; with 4-Å MS) was added isovaleraldehyde (33 µl, 0.3 mmol), the mixture was stirred for 10 min, then (*E*)-3,3-dimethyl-1-nitrobut-1-ene (38.75 mg, 0.3 mmol) was added, and the mixture was stirred at r.t. for 3 d (monitored by TLC). Then, hexane was added, and the mixture was filtered. From the clear soln., crystallization took place to give **4q** (133 mg, 85%). Colorless crystals, suitable for X-ray analysis. M.p. 138–144° (dec). $[\alpha]^{25}_{D} = -10.1$ (c = 0.80, $CHCl_3$). ^{1}H-NMR (500 MHz, C_6D_6): 7.70 (br. *s*, 2 H); 7.61 (*d*, J = 7.0, 2 H); 7.21–7.13 (*m*, 5 H); 7.09 (*t*, J = 7.5, 1 H); 4.90 (*t*, J = 7.5, 1 H); 4.41 (*t*, J = 5.5, 1 H); 4.19 (br. *s*, 1 H); 2.45–2.41 (*m*, 2 H); 2.32 (*t*, J = 9.5, 1 H); 1.94–1.85 (*m*, 2 H); 1.73 (*td*, J = 10.0, 3,5, 1 H); 1.57 (br. *s*, 1 H); 1.19–1.15 (*m*, 1 H); 0.82 (d, J = 7.0, 3 H); 0.87–0.73 (*m*, 3 H); 0.66 (s, 9 H); 0.38–0.49 (*m*, 1 H); –0.04 (*s*, 9 H); ^{13}C-NMR (75 MHz, C_6D_6): 143.5; 142.8; 130.2; 130.0; 127.3; 78.8; 69.4; 62.8; 49.5; 47.6; 42.4; 32.0; 29.4; 29.6; 29.2; 27.4; 24.0; 21.4; 18.0; 2.4. Anal. calc. for $C_{31}H_{46}N_2O_3Si$ (522.80): C 71.22, H 8.87, N 5.36; found: C 71.16, H 8.77, N 5.36.

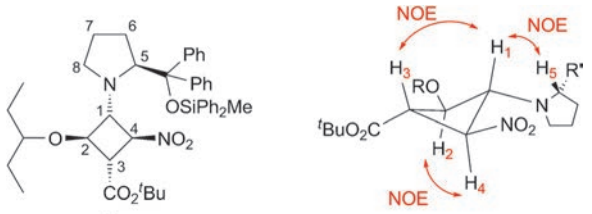
3.4. *Thermal Stability of Cyclobutane* **4q**. To the soln. of **4q** (18.3 mg, 0.035 mmol) in (D_8)toluene (0.6 ml) in an NMR tube in the presence of 4-Å MS, β-nitrostyrene (5.2 mg, 0.035 mmol) was added, and the NMR tube was sealed. The mixture was heated for 30 min each at 60°, 70°, 80°, 90°, 100°, 110°, 120°, followed by cooling to r.t., then ^{1}H-NMR was recorded. Up to 80° no change, at 90° traces of the enamine precursor, and after heating to 120° the cyclobutane **4e** were detected.

3.5. *Hydrolytic Stability of the Cyclobutane* **4q**. To the soln. of **4q** (26.1 mg, 0.05 mmol) in (D_8)toluene (0.6 ml) in an NMR tube in the presence of 10.0 equiv. H_2O, 4-nitrophenol (0.7 mg, 10 mol-%) was added, and the composition of the mixture was monitored by ^{1}H-NMR. After 24 h, no corresponding nitro aldehyde was detected, cyclobutane **4q** was stable under this conditions.

4. *Reactions of Enamines from 2-(Isopentyloxy)acetaldehyde with 3-Nitroacrylate and 3-Acetamidonitroethene.* 4.1. *Formation of* **4h**, **4i**, *and* **6h**. To a 5 ml flask with 4-Å MS (440 mg, pellets) were added

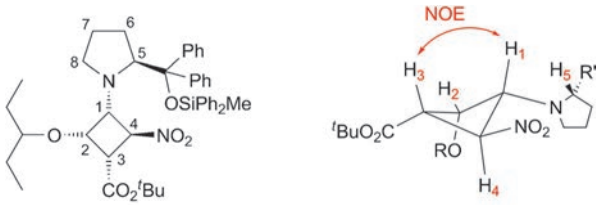
C_6D_6 (0.2 ml), a stock soln. of **1b** (0.05 mmol, 0.25 ml, 0.2M in C_6D_6), a stock soln. of *2-(pentan-3-yloxy)acetaldehyde* (**9**; 0.05 mmol, 0.25 ml, 0.2M in C_6D_6), and a stock soln. of toluene (0.02 mmol, 40 µl, 0.5M in C_6D_6) at r.t. In another flask, a further sample was prepared following exactly the same procedure. The two flasks were kept for 4 h at r.t. for the enamine formation. An NMR sample was prepared from one of the solns. to determine the (*E*)/(*Z*)-enamine ratio: (*E*)-**10a**/(*Z*)-**10a**/toluene 1 : 1.55 : 1.84. Calculation of the generated enamine **10a**: enamine (1 + 1.55) × toluene (0.02 mmol)/1.84 = 0.028 mmol. To the other sample was added a stock soln. of *tert*-butyl (*E*)-3-nitroacrylate (0.028 mmol, 0.28 ml, 0.1M in C_6D_6) at r.t. Then, 0.55 ml of this sample was transferred to an NMR tube. The formation of **4h**, **4i**, and **6h** was monitored by ^{1}H-NMR spectroscopy, and the progress (concentration *vs.* time) was plotted (*Fig. 6*).

tert-*Butyl (1*S*,2*S*,3*R*,4*R*)-3-{(2*S*)-2-[{[Methyl(diphenyl)silyl]oxy}(diphenyl)methyl]pyrrolidin-1-yl}-2-nitro-4-(pentan-3-yloxy)cyclobutanecarboxylate* (**4h**). ^{1}H-NMR (300 MHz, C_6D_6): 7.75 – 6.95 (*m*, 20 H); 5.07 (*t*, *J* = 7.6, H(4)); 4.61 (*dd*, *J* = 8.6, 3.4, H(5)); 4.35 – 4.21 (br., H(1)); 3.81 (*t*, *J* = 7.6, H(2)); 3.27 (*t*, *J* = 7.6, H(3)); 3.22 – 3.12 (*m*, 1 H); 2.45 – 2.34 (*m*, 2 H); 2.05 – 1.89 (*m*, 2 H); 1.46 – 1.34 (*m*, 5 H); 1.26 (*s*, 9 H); 0.92 – 0.78 (*m*, 7 H); 0.24 (*s*, 3 H). ^{13}C-NMR (100 MHz, C_6D_6): 73.9 (C(2)); 73.9 (C(4)); 70.3 (C(1)); 68.4 (C(5)); 48.0 (C(3)). NOESY (400 MHz, C_6D_6, 7°). COSY: H(1)/H(2), H(2)/H(3), H(3)/H(4), H(4)/H(1). HMBC: C(1)/H(5).



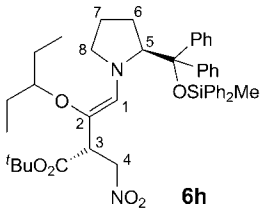
4h

tert-*Butyl (1*S*,2*S*,3*R*,4*S*)-3-{(2*S*)-2-[{[Methyl(diphenyl)silyl]oxy}(diphenyl)methyl]pyrrolidin-1-yl}-2-nitro-4-(pentan-3-yloxy)cyclobutanecarboxylate* (**4i**). ^{1}H-NMR (300 MHz, C_6D_6): 7.73 – 6.98 (*m*, 20 H); 5.96 (*t*, *J* = 8.8, H(4)); 4.35 (*dd*, *J* = 9.0, 4.2, H(5)); 4.30 – 4.21 (br., 1 H, H(1)); 3.73 (*t*, *J* = 6.6, H(2)); 3.19 (*dd*, *J* = 8.8, 6.6, H(3)); 3.14 – 3.07 (*m*, 1 H); 2.62 – 2.48 (*m*, 2 H); 2.03 – 1.88 (*m*, 2 H); 1.57 – 1.38 (*m*, 5 H); 1.35 (*s*, 9 H); 0.92 – 0.75 (*m*, 7 H); 0.30 (*s*, 3 H). NOESY (500 MHz, (D_8)toluene, 0°). COSY: H(1)/H(2), H(2)/H(3), H(3)/H(4), H(4)/H(1).



4i

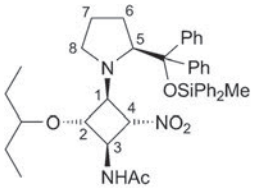
tert-*Butyl (2*S*,3*Z*)-4-{(2*S*)-2-[{[Methyl(diphenyl)silyl]oxy}(diphenyl)methyl]pyrrolidin-1-yl}-2-(nitromethyl)-3-(pentan-3-yloxy)but-3-enoate* (**6h**). ^{1}H-NMR (300 MHz, C_6D_6): 7.74 – 6.98 (*m*, 20 H); 5.22 (*s*, H(1)); 4.46 – 4.33 (*m*, H(4)); 4.10 (*dd*, *J* = 8.3, 3.2, H(5)); 3.75 – 3.60 (*m*, H(4)); 3.23 – 3.10 (*m*, H(3)); 3.03 – 2.91 (*m*, 1 H); 2.60 – 2.47 (*m*, 2 H); 2.04 – 1.90 (*m*, 2 H); 1.53 – 1.38 (*m*, 5 H); 1.36 (*s*, 9 H); 0.91 – 0.78 (*m*, 7 H); 0.20 (*s*, 3 H). HSQC: H(1) (δ 5.22)/C(1) (δ 127.5).



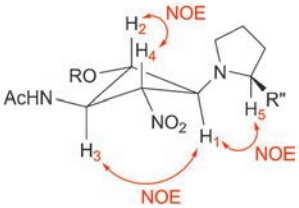
6h

4.2. *Formation of* **4j** *and* **6j**. To a 5 ml flask with 4-Å MS (440 mg, pellets) were added at r.t. C_6D_6 (0.2 ml), a stock soln. of **1b** (0.04 mmol, 0.20 ml, 0.2M in C_6D_6), a stock soln. of 2-(pent-3-yloxy)acetaldehyde (**9**; 0.04 mmol, 0.20 ml, 0.2M in C_6D_6), and a stock soln. of toluene (0.016 mmol, 32 µl, 0.5M in C_6D_6). In another flask, a further sample was prepared following exactly the same procedure. The two flasks were kept for 4 h at r.t. for the enamine formation. An NMR sample was prepared from one of the solns. to determine the (*E*)/(*Z*)-enamine ratio; (*E*)-**10a**/(*Z*)-**10a**/toluene 1 : 1.58 : 1.76. Calculation of the generated enamine **10a**: enamine (1 + 1.58) × toluene (0.016 mmol)/1.76 = 0.024 mmol. To the other sample was added a stock soln. of *N*-[(*Z*)-2-nitroethenyl]acetamide (0.024 mmol, 0.47 ml, 0.05M in C_6D_6) at r.t.. Then 0.60 ml of this sample was transferred to an NMR tube. The formation of **4j** and **6j** was monitored by ^{1}H-NMR spectroscopy, and the progress (concentration *vs.* time) was plotted (*Fig. 7*).

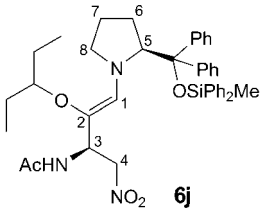
N-*[(1*R*,2*R*,3*S*,4*S*)-3-{(2*S*)-2-[{[Methyl(diphenyl)silyl]oxy}(diphenyl)methyl]pyrrolidin-1-yl}-2-nitro-4-(pentan-3-yloxy)cyclobutyl]acetamide* (**4j**). ^{1}H-NMR (300 MHz, C_6D_6): 7.74 – 6.88 (*m*, 20 H); 5.20 (*t*, *J* = 8.0, H(4)); 4.73 (*t*, *J* = 7.2, H(2)); 4.55 (*dd*, *J* = 8.8, 3.6, H(5)); 4.38 (*d*, *J* = 6.8, NH); 3.83 (br., H(1)); 3.36 (*ddd*, *J* = 8.0, 7.2, 6.8, H(3)); 3.05 – 2.96 (*m*, 1 H); 2.63 – 2.40 (*m*, 2 H); 2.04 – 1.75 (*m*, 2 H); 1.58 – 1.34 (*m*, 5 H); 1.28 (*s*, 3 H); 0.98 – 0.76 (*m*, 7 H), 0.30 (*s*, 3 H). NOESY (500 MHz, C_6D_6, 15°). COSY: H(1)/H(2), H(2)/H(3), H(3)/H(4), H(4)/H(1).



4j



N-*[(2*R*,3*Z*)-4-{(2*S*)-2-[{[Methyl(diphenyl)silyl]oxy}(diphenyl)methyl]pyrrolidin-1-yl}-1-nitro-3-(pentan-3-yloxy)but-3-en-2-yl]acetamide* (**6j**). ^{1}H-NMR (400 MHz, C_6D_6): 7.74 – 6.97 (*m*, 20 H); 5.35 (*s*, H(1)); 4.21 (*dd*, *J* = 12.0, 6.0, H(4)); 4.08 (*dd*, *J* = 8.8, 4.0, H(5)); 3.99 – 3.93 (*m*, H(4)); 3.91 – 3.87 (*m*, H(3)); 3.06 – 2.98 (*m*, 1 H); 2.55 – 2.40 (*m*, 2 H); 1.99 – 1.77 (*m*, 2 H); 1.60 – 1.46 (*m*, 5 H); 1.44 (*s*, 3 H); 0.94 – 0.72 (*m*, 7 H); 0.22 (*s*, 3 H). ^{13}C-NMR (100 MHz, C_6D_6): 127.3 (C(1)); 78.9 (C(3)); 77.0 (C(4)); 74.3 (C(5)). HMBC: C(1)/H(5).



6j

5. *Preparation, Identification, and Reactivity of Oxazine Derivatives* **5**. 5.1. *Preparation of* **5b** – **5f** *and* **5h**. *(4*S*,5*R*,6*R*)-6-[(2*S*)-2-{Diphenyl[(trimethylsilyl)oxy]methyl}pyrrolidin-1-yl]-5,6-dihydro-3,5-dimethyl-4-phenyl-4*H*-1,2-oxazine 2-Oxide* (**5b**). Prepared according to *GP* from **1a** (32.6 mg, 0.1 mmol),

propanal (7.2 µl, 0.1 mmol), and (*E*)-*β*-methyl-*β*-nitrostyrene (16.3 mg, 0.1 mmol; $t \leq 10$ min). After complete reaction, the soln. was filtered and concentrated to afford the crude product. Crystallization from hexane yielded **5b** (38 mg, 72%). Colorless crystals, suitable for X-ray analysis. M.p. 120–121° (dec). $[\alpha]^{23}_{D} = -13.4$ ($c = 0.83$, $CHCl_3$). IR (neat): 2965*m*, 1611*m*, 1493*w*, 1447*w*, 1374*w*, 1249*m*, 1138*w*, 1089*w*, 1056*m*, 878*m*, 833*s*, 787*m*, 771*m*, 747*m*, 699*s*. ^{1}H-NMR (400 MHz, C_6D_6): 7.51–7.49 (*m*, 2 H); 7.42–7.40 (*m*, 2 H); 7.16 (*s*, 5 H); 7.12–7.09 (*m*, 2 H); 7.05–7.01(*m*, 2 H); 6.83 (*dd*, *J* = 2.0, 8.0, 2 H); 5.38 (*d*, *J* = 6.8, 1 H); 4.80 (*dd*, *J* = 3.2, 9.6, 1 H); 2.96–2.89 (*m*, 2 H); 2.19–2.15 (*m*, 1 H); 2.09–1.97 (*m*, 2 H); 1.75 (*d*, *J* = 1.2, 3 H); 1.71–1.65(*m*, 1 H); 1.35–1.29 (*m*, 1 H); 0.88 (*d*, *J* = 6.4, 3 H); 0.64–0.59 (*m*, 1 H); −0.04 (*s*, 9 H). ^{1}H-NMR (300 MHz, C_6D_6) of **5b** at 50° in the presence of 4-Å MS was recorded, and compared to that recorded at r.t., there were no changes (*cf. Table 4*). ^{13}C-NMR (100 MHz, C_6D_6): 144.0; 141.3; 130.2; 130.2; 129.2; 128.6; 128.2; 127.9; 127.7; 127.6; 127.4; 127.1; 119.3; 100.4; 85.4; 67.7; 54.4; 45.4; 41.9; 29.1; 24.5; 17.1; 15.2; 2.2. HR-ESI-MS: 529.2881 ($[M+H]^+$, $C_{32}H_{41}N_2O_3Si^+$; calc. 529.2881 (err., 0.0 ppm)). Anal. calc. for $C_{32}H_{40}N_2O_3Si$ (528.77): C 72.69, H 7.62, N 5.30; found: C 72.85, H 7.59, N 5.24.

*(4*S*,5*R*,6*R*)-6-[(2*S*)-2-{Diphenyl[(trimethylsilyl)oxy]methyl}pyrrolidin-1-yl]-5,6-dihydro-3-methyl-4-phenyl-5-propyl-4*H*-1,2-oxazine 2-Oxide* (**5c**). Prepared according to *GP* from **1a** (32.6 mg, 0.1 mmol), valeraldehyde (10.6 µl, 0.1 mmol), and (*E*)-*β*-methyl-*β*-nitrostyrene (16.3 mg, 0.1 mmol) ($t \leq 10$ min). After completion of the reaction, the soln. was filtered and concentrated to afford the crude product. Crystallization from hexane yielded **5c** (35 mg, 63%). Colorless crystals, suitable for X-ray analysis. M.p. 130–131° (dec). ^{1}H-NMR (400 MHz, C_6D_6): 7.50 (*dd*, *J* = 2.0, 8.4, 2 H); 7.44–7.42 (*m*, 2 H); 7.15 (*s*, 5 H); 7.11–7.07 (*m*, 2 H); 7.03–7.00 (*m*, 2 H); 6.93–6.90 (*m*, 2 H); 5.39 (*d*, *J* = 7.6, 1 H); 4.86 (*dd*, *J* = 3.2, 9.6, 1 H); 3.06 (*d*, *J* = 8.0, 1 H); 2.96 (*q*, *J* = 8.8, 1 H); 2.25–2.15 (*m*, 2 H); 2.10–1.99 (*m*, 1 H); 1.80–1.72 (*m*, 1 H); 1.75 (*d*, *J* = 1.2, 3 H); 1.53–1.43 (*m*, 1 H); 1.39–1.31 (*m*, 1 H); 1.29–1.20 (*m*, 1 H); 1.11–0.88(*m*, 2 H); 0.75 (*t*, *J* = 7.2, 3 H); 0.65–0.55 (*m*, 1 H); −0.05 (*s*, 9 H). ^{1}H-NMR (300 MHz, C_6D_6) of **5c** at 50° in the presence of 4-Å MS was recorded, and compared to that recorded at r.t., there were no changes (*cf. Table 4*). ^{13}C-NMR (100 MHz, C_6D_6): 144.1; 143.8; 142.2; 130.2; 130.2; 129.2; 128.6; 127.9; 127.7; 127.7; 127.5; 127.5; 127.3; 120.1; 100.4; 85.2; 68.4; 51.9; 46.5; 46.3; 32.8; 29.2; 24.7; 19.5; 17.0; 14.6; 2.3. HR-ESI-MS: 557.3189 ($[M+H]^+$, $C_{34}H_{45}N_2O_3Si^+$; calc. 557.3194 (err., 0.9 ppm)).

*(4*S*,5*R*,6*R*)-6-[(2*S*)-2-{Diphenyl[(trimethylsilyl)oxy]methyl}pyrrolidin-1-yl]-5,6-dihydro-5-isopropyl-3-methyl-4-phenyl-4*H*-1,2-oxazine 2-Oxide* (**5d**). Prepared according to *GP* from **1a** (32.6 mg, 0.1 mmol), isovaleraldehyde (10.8 µl, 0.1 mmol), and (*E*)-*β*-methyl-*β*-nitrostyrene (16.3 mg, 0.1 mmol; *t* 2 h, >85% conversion). After completed reaction, the soln. was filtered and concentrated to afford the crude product. Crystallization from hexane yielded **5d** (38 mg, 68%). Colorless crystals (moisture-sensitive), suitable for X-ray analysis. IR (neat): 2956*w*, 1614*m*, 1493*w*, 1447*w*, 1406*w*, 1341*w*, 1248*m*, 1218*w*, 1090*w*, 1056*m*, 1032*w*, 939*w*, 909*w*, 882*m*, 836*s*, 702*s*. ^{1}H-NMR (600 MHz, C_6D_6): 7.63–7.50 (*m*, 5 H); 7.13 −7.03 (*m*, 9 H); 7.00–6.97 (*m*, 1 H); 5.45 (br. *s*, 1 H); 5.01 (*dd*, *J* = 3, 9.6, 1 H); 3.19 (*s*, 1 H); 2.92 (*m*, 1 H); 2.43 (*m*, 1 H); 2.29–2.24 (*m*, 1 H); 2.10–2.07 (*m*, 1 H); 1.95–1.84 (*m*, 2 H); 1.80 (*s*, 3 H); 1.30–1.23 (*m*, 1 H); 0.71 (br. *s*, 3 H); 0.65 (*d*, *J* = 6.6, 3 H); 0.55–0.46 (*m*, 1 H); −0.05 (*s*, 9 H). HR-ESI-MS: 557.3209 ($[M+H]^+$, $C_{34}H_{45}N_2O_3Si^+$; calc. 557.3194 (err., −2.7 ppm)). Measurement of the temp.-dependent equilibrium of **5d** with the corresponding enamine **2** and nitro olefin **3**: ^{1}H-NMR (300 MHz, C_6D_6) of **5d** in the presence of 4-Å MS was recorded at r.t., **5d**/enamine **2** 7:1; at 50°, **5d**/enamine **2** 1.5:1; cooling the sample to r.t., after further 2 h, **5d**/enamine **2** 7:1 (*cf. Table 4*).

*(4*R*,5*R*,6*R*)-6-[(2*S*)-2-{Diphenyl[(trimethylsilyl)oxy]methyl}pyrrolidin-1-yl]-5,6-dihydro-4,5-diisopropyl-3-methyl-4*H*-1,2-oxazine 2-Oxide* (**5e**). To a soln. of **1a** (65.1 mg, 0.2 mmol) in benzene (0.1 ml, with 4-Å MS) was added isovaleraldehyde (21.6 µl, 0.2 mmol), the mixture was stirred for 10 min, then (*E*)-3-methyl-1-nitrobut-1-ene (23.0 mg, 0.2 mmol) was added, and stirring at r.t. was continued for 90 h. Purification by prep. TLC (hexane/AcOEt, 3:1) afforded **5e** (46 mg, 44%). $[\alpha]^{25}_{D} = -47.7$ ($c = 1.0$, $CHCl_3$). IR (neat): 2958*m*, 2873*w*, 1724*w*, 1608*m*, 1493*w*, 1463*w*, 1410*w*, 1249*m*, 1091*m*, 1063*m*, 879*m*, 837*s*, 749*m*, 702*s*. ^{1}H-NMR (300 MHz, C_6D_6): 7.69–7.62 (*m*, 4 H); 7.04–7.23 (*m*, 6 H); 5.08 (*d*, *J* = 10.5, 1 H); 4.95 (*dd*, *J* = 3.0, 9.0, 1 H); 3.10–2.94 (*m*, 1 H); 2.55–2.48 (*m*, 1 H); 2.15–2.10 (*m*, 3 H); 1.94 (*s*, 3 H); 1.86–1.80 (*m*, 1 H); 1.54 −1.47 (*m*, 1 H); 1.36–1.31 (*m*, 1 H); 0.98–0.90 (*m*, 1 H); 0.75–0.70 (*m*, 9 H); 0.65–0.56 (*m*, 1 H); 0.44 (*d*, *J* = 5.7, 3 H); −0.04 (*s*, 9 H). ^{13}C-NMR (100 MHz, C_6D_6): 144.1; 143.4; 130.5; 130.0; 128.2; 127.9; 127.7; 127.4; 127.3; 124.7; 102.6; 84.8; 69.2; 49.5; 47.4; 47.3; 33.5; 28.1; 25.1; 24.6;

21.5; 21.4; 20.6; 19.2; 17.2; 2.3. HR-ESI-MS: 523.3368 ($[M+H]^+$, $C_{31}H_{47}N_2O_3Si^+$; calc. 523.3350 (err., −3.3 ppm)).

*(3*R*,4*R*,4a*R*)-3-[(2*S*)-2-{Diphenyl[(trimethylsilyl)oxy]methyl}pyrrolidin-1-yl]-4,4a,5,6,7,8-hexahydro-4-isopropyl-3*H*-2,1-benzoxazine 1-Oxide* (**5f**). Prepared according to *GP* from **1a** (32.6 mg, 0.1 mmol), isovaleraldehyde (10.8 µl, 0.1 mmol), and 1-nitrocyclohexene (12.7 mg, 0.1 mmol; *t* 16 h, 50% conversion). ^{1}H-NMR (400 MHz, C_6D_6): 7.57–7.44 (*m*, 4 H); 7.15–7.04 (*m*, 6 H); 5.24 (br. *s*, 1 H); 4.91 (*dd*, *J* = 2.8, 9.2, 1 H); 3.40 (*d*, *J* = 14.0, 1 H); 2.90 (*q*, *J* = 8.4, 1 H); 2.25–2.18 (*m*, 1 H); 2.10–2.04 (*m*, 1 H); 2.04–1.94 (*m*, 2 H); 1.90–1.82 (*m*, 1 H); 1.80–1.75 (*m*, 1 H); 1.73–1.65 (*m*, 2 H); 1.61–1.57 (*m*, 1 H); 1.46 −1.51 (*m*, 2 H); 1.33–1.24 (*m*, 3 H); 0.98–0.96 (*m*, 3 H); 0.77 (*d*, *J* = 6.8, 3 H); 0.58–0.48 (*m*, 1 H); −0.10 (*s*, 9 H). Measurement of the temp.-dependent equilibrium of **5f** with the corresponding enamine **2** and nitro olefin **3**: ^{1}H-NMR (300 MHz, C_6D_6) of **5f** in the presence of 4-Å MS was recorded at r.t., **5f**/enamine **2** 1:1; at 50°, **5f**/enamine **2** 1:3; cooling the sample back to r.t., after further 2 h, **5f**/enamine **2** 1:1 (*cf. Table 4*).

*Ethyl (4*R*,5*R*,6*R*)-6-[(2*S*)-2-{Diphenyl[(trimethylsilyl)oxy]methyl}pyrrolidin-1-yl]-5,6-dihydro-3-methyl-5-propyl-4*H*-1,2-oxazine-4-carboxylate 2-Oxide* (**5h**). Prepared according to *GP* from **1a** (32.6 mg, 0.1 mmol), valeraldehyde (10.6 µl, 0.1 mmol), and ethyl (*E*)-3-nitrobut-2-enoate (15.9 mg, 0.1 mmol) in the presence of 3-Å MS ($t \leq 10$ min, >90%). ^{1}H-NMR (600 MHz, C_6D_6): 7.48 (*d*, *J* = 7.2, 2 H); 7.40–7.39 (*m*, 2 H); 7.12–7.05 (*m*, 6 H); 5.23 (br. *s*, 1 H); 4.74 (*dd*, *J* = 2.4, 9.0, 1 H); 3.86–3.82 (*m*, 2 H); 3.05 (*q*, *J* = 7.8, 1 H); 2.91 (*s*, 2 H); 2.37 (br. *s*, 1 H); 2.02 (*s*, 3 H); 1.97–1.91 (*m*, 1 H); 1.74–1.66 (*m*, 1 H); 1.57–1.52 (*m*, 1 H); 1.29–1.12 (*m*, 4 H); 0.90 (*t*, *J* = 6.0, 3 H); 0.84 (*t*, *J* = 7.2, 3 H); 0.63–0.58 (*m*, 1 H); −0.10 (*s*, 9 H). ^{1}H-NMR (300 MHz, C_6D_6) of **5h** at 50° in the presence of 3-Å MS was recorded, and compared to that recorded at r.t., there were no changes (*cf. Table 4*). ^{13}C-NMR (100 MHz, C_6D_6): 170.6; 144.0; 143.8; 130.1; 128.5; 127.7; 127.7; 127.4; 127.2; 116.8; 102.3; 85.3; 68.5; 61.6; 51.3; 46.5; 41.7; 34.2; 29.2; 24.6; 19.8; 17.1; 14.5; 2.2.

5.2. *Deuterolysis of Oxazine Derivative* **5b**. To a $CDCl_3$ soln. (0.3 ml) of **1a** (19 mg, 0.058 mmol) in an NMR tube, propanal (4.2 µl, 0.058 mmol) in $CDCl_3$ (0.29 ml, 0.2M) and 3-Å MS (3 mm high) were added at r.t. After confirming the generation of enamine by NMR, (*E*)-β-methyl-β-nitrostyrene (9.5 mg, 0.058 mmol) was added. After confirming the generation of **5b**, the mixture was transferred to another dry NMR tube *via* syringe (without 3-Å MS). D_2O (1.8 µl, 0.088 mmol) and 4-NO_2–C_6H_4OD (33 mg, 0.234 mmol, D: 81%) were added to the NMR tube. The reaction was monitored by ^{1}H-NMR, and the results are collected in *Table 6*; they show that there is D incorporation mainly in the α-position of the γ-nitro aldehyde **7r**.

Table 6. *Deuterolysis of* **5b**. Ratios determined by NMR peak integration.

Time [h]	**5b** [%]	**7r** [%]	Diastereoisomers [%]
0.5	89	6	5
1.5	81	14 (D: α > 50%, γ < 10%)	5
3	69	23 (D: α > 50%, γ < 10%)	8
6	57	34 (D: α > 50%, γ < 10%)	9
17	41	49 (D: α > 50%, γ < 10%)	10

6. *Formation of the Nitro Enamines* **6** *and Their Reactions*. 6.1. *Formation of* **6a**, **6c**–**6e**, **6g**, **6r**, *and* **6s**. *(2*S*)-2-{Diphenyl[(trimethylsilyl)oxy]methyl}-1-[(1*E*,3*R*)-2-methyl-4-nitro-3-phenylbut-1-en-1-yl]pyrrolidine* (**6a**). *Method 1*. According to *GP*, a mixture **4a**/**5a** 4:1 was prepared from **1a** (32.6 mg, 0.1 mmol), propanal (7.2 µl, 0.1 mmol) and β-nitrostyrene (14.9 mg, 0.1 mmol), and its composition monitored by ^{1}H-NMR. After 15 h, **6a** formed quantitatively (>99% conversion). FC purification failed due to decomposition.

Method 2. In an NMR tube, a soln. of **1a** (32.6 mg, 0.1 mmol) in CD_2Cl_2 (0.6 ml) with MS (4 Å) was prepared, and propanal (7.2 µl, 0.1 mmol) was added; the composition of the mixture was monitored by

^{1}H-NMR. After enamine formation, β-nitrostyrene (14.9 mg, 1.0 equiv.) was added, and the reaction was monitored by ^{1}H-NMR again; **6a** formed within 10 min (conversion >98%).

Method 3. To a flask with 3-Å MS were added benzene (1 ml), **1a** (325 mg, 1.0 mmol) in benzene (1.5 ml), and propanal (79 µl, 1.1 mmol) at r.t. The mixture was stirred for 5 min at r.t., and an aliquot was taken for NMR recording. After confirming the generation of enamine, β-nitrostyrene (149 mg, 1.0 mmol) was added. The mixture was stirred for 5 min, filtered with a syringe filtration device, the solvent was removed under reduced pressure, and the residue was dried under vacuum for 2 h. CH_2Cl_2 (5 ml) was added to the residue, and the soln. was stirred for 15 min. The solvent was evaporated *in vacuo*, and the residue was dried under reduced pressure to afford **6a** (432 mg, 84%). Yellow oil. ^{1}H-NMR (400 MHz, C_6D_6): 7.56–7.49 (*m*, 2 H); 7.45–7.42 (*m*, 2 H); 7.17–7.03 (*m*, 9 H); 6.72 (*d*, *J* = 6.8, 2 H); 5.97 (*s*, 1 H); 4.26–4.19 (*m*, 2 H); 4.05 (*dd*, *J* = 5.2, 8.4, 1 H); 3.91 (*dd*, *J* = 6.0, 9.6, 1 H); 2.71–2.67 (*m*, 2 H); 1.79–1.65 (*m*, 2 H); 1.35 (*s*, 3 H); 1.23–1.13 (*m*, 1 H); 0.75–0.66 (*m*, 1 H); −0.09 (*s*, 9 H). ^{13}C-NMR (100 MHz, C_6D_6): 144.2; 142.9; 140.9; 130.3; 129.9; 129.1; 129.0; 128.6; 127.6; 127.6; 127.3; 127.2; 127.1; 110.3; 84.2; 78.1; 73.0; 55.5; 50.7; 28.2; 24.7; 12.8; 2.2.

*(2*S*)-2-{Diphenyl[(trimethylsilyl)oxy]methyl}-1-{(1*E*)-2-[(1*R*)-2-nitro-1-phenylethyl]hex-1-en-1-yl}-pyrrolidine* (**6c**). According to *GP*, a soln. of **4c** was prepared from **1a** (32.6 mg, 0.1 mmol), hexanal (12.3 µl, 0.1 mmol), and β-nitrostyrene (14.9 mg, 0.1 mmol); monitoring by ^{1}H-NMR indicated conversion at r.t. to **6c**. ^{1}H-NMR (400 MHz, C_6D_6): 5.90 (*s*, 1 H); 4.31–4.26 (*m*, 1 H); 4.18 (*dd*, *J* = 7.6, 11.6, 1 H); 4.12–4.09 (*m*, 1 H); 4.03 (*t*, *J* = 8.0, 1 H); 2.83–2.78 (*m*, 1 H); 2.62 (*dd*, *J* = 7.6, 16.0, 1 H); 2.05–1.97 (*m*, 1 H); 1.78 (*dd*, J = 6.8, 14.0, 2 H); 1.73–1.66 (*m*, 1 H); 1.27–1.16 (*m*, 2 H); 1.14–1.07 (*m*, 2 H); 1.05–0.94 (*m*, 1 H); 0.79 (*t*, *J* = 7.2, 3 H); 0.71–0.61 (*m*, 1 H); −0.02 (*s*, 9 H).

*(2*S*)-1-{(1*E*)-5-(Benzyloxy)-2-[(1*R*)-2-nitro-1-phenylethyl]pent-1-en-1-yl}-2-{diphenyl[(trimethylsilyl)oxy]methyl}pyrrolidine* (**6d**). According to *GP*, a soln. of **4d** was prepared from **1a** (32.6 mg, 0.1 mmol), 5-(benzyloxy)pentanal (19.2 mg, 0.1 mmol), and β-nitrostyrene (14.9 mg, 0.1 mmol); monitoring by ^{1}H-NMR indicated conversion at r.t. to **6d**. ^{1}H-NMR (400 MHz, C_6D_6): 7.81–6.85 (*m*, 20 H); 6.01 (*s*, 1 H); 4.32 (*s*, 2 H); 4.29–4.03 (*m*, 3 H); 3.27–3.09 (*m*, 2 H); 3.01–2.91 (*m*, 1 H); 2.77–2.61 (*m*, 1 H); 2.28–2.19 (*m*, 1 H); 1.98–1.17 (*m*, 7 H); 0.77–0.63 (*m*, 1 H); 0.02 (*s*, 9 H).

*(2*S*)-2-{Diphenyl[(trimethylsilyl)oxy]methyl}-1-[(1*E*,3*R*)-2-isopropyl-4-nitro-3-phenylbut-1-en-1-yl]pyrrolidine* (**6e**). According to *GP*, a soln. of **4e** was prepared from **1a** (32.6 mg, 0.1 mmol), isovaleraldehyde (10.8 µl, 0.1 mmol), and β-nitrostyrene (14.9 mg, 0.1 mmol); monitoring by ^{1}H-NMR showed 29% conversion after 24 h at r.t., with formation of **6e**. ^{1}H-NMR (400 MHz, C_6D_6): 8.00–6.60 (*m*, 15 H); 5.65 (*s*, 1 H); 4.19 (*dd*, *J* = 7.2, 8.8, 1 H); 4.20–4.00 (*m*, 2 H); 2.96 (*dt*, *J* = 6.8, 14.0, 1 H); 2.80–2.60 (*m*, 1 H); 2.55 (*ddd*, *J* = 5.6, 8.0, 9.6, 1 H); 2.0–1.60 (*m*, 2 H); 1.18–1.10 (*m*, 1 H); 0.97 (*d*, *J* = 6.8, 3 H); 0.70 (*d*, *J* = 6.8, 3 H); 1.40–0.40 (*m*, 2 H); −0.06 (*s*, 9 H).

tert-*Butyl (2*R*,3*E*)-3-{[(2*S*)-2-{Diphenyl[(trimethylsilyl)oxy]methyl}pyrrolidin-1-yl]methylidene}-4-methyl-2-(nitromethyl)pentanoate* (**6g**). According to *GP*, a soln. of **4g** was prepared from **1a** (32.6 mg, 0.1 mmol), isovaleraldehyde (10.8 µl, 0.1 mmol), and *tert*-butyl (*E*)-3-nitroacrylate (17.3 mg, 0.1 mmol), monitoring by ^{1}H-NMR showed after 40 h >90% conversion to **6g**. ^{1}H-NMR (C_6D_6, 400 MHz): 7.63–6.99 (*m*, 10 H); 5.81 (*s*, 1 H); 4.70 (*dd*, *J* = 2.4, 9.6, 1 H); 4.39 (*dd*, *J* = 9.6, 13.6, 1 H); 4.01 (*dd*, *J* = 6.2, 8.2, 1 H); 3.51 (*dd*, *J* = 3.0, 12.2, 1 H); 2.83–2.75 (*m*, 1 H); 2.73–2.61 (*m*, 2 H); 1.82–1.62 (*m*, 4 H); 1.31 (*s*, 9 H); 1.05 (*d*, *J* = 7.2, 3 H); 0.68 (*d*, *J* = 7.2, 3 H); −0.05 (*s*, 9 H).

*(2*S*)-2-{Diphenyl[(trimethylsilyl)oxy]methyl}-1-[(1*E*,3*R*,4*R*)-2-methyl-4-nitro-3-phenylpent-1-en-1-yl]pyrrolidine* (**6r**). To a soln. of **1a** (18.9 mg, 0.058 mmol) in (D_8)toluene (0.6 ml) with MS (3 Å) in an NMR tube was added nitro aldehyde **7r** [12] (12.8 mg, 0.058 mmol), and the reaction was monitored by ^{1}H-NMR; **6r** was formed within 10 min (conversion >90%) at r.t. ^{1}H-NMR (400 MHz, (D_8)toluene): 7.48–7.45 (*m*, 2 H); 7.40–7.37 (*m*, 2 H); 7.10–6.93 (*m*, 11 H); 5.95 (*s*, 1 H); 4.92–4.84 (*m*, 1 H); 4.11 (*dd*, *J* = 5.2, 8.4, 1 H); 3.65 (*d*, *J* = 10.8, 1 H); 2.67–2.62 (*m*, 1 H); 2.51–2.46 (*m*, 1 H); 1.88–1.71 (*m*, 2 H); 1.27 (*d*, *J* = 6.8, 3 H); 1.19 (*d*, *J* = 0.8, 3 H); 1.23–1.14 (*m*, 1 H); 0.76–0.66 (*m*, 1 H); −0.11 (*s*, 9 H). ^{13}C-NMR (100 MHz, (D_8)toluene): 144.4; 143.0; 141.1; 140.4; 130.5; 130.2; 128.8; 128.1; 128.1; 128.0; 127.6; 127.5; 127.4; 111.9; 84.5; 84.4; 73.3; 57.3; 55.9; 28.7; 25.2; 19.8; 13.4; 2.5.

*Ethyl (2*R*,3*E*)-3-{[(2*S*)-2-{Diphenyl[(trimethylsilyl)oxy]methyl}pyrrolidin-1-yl]methylidene}-2-[(1*R*)-1-nitroethyl]hexanoate* (**6s**). According to *GP*, a soln. of **5h** was prepared from **1a** (32.6mg, 0.1 mmol), valeraldehyde (10.6 µl, 0.1 mmol), and ethyl (*E*)-3-nitrobut-2-enoate (15.9 mg, 0.1 mmol) in

the presence of MS (3 Å); monitoring by ^{1}H-NMR showed conversion (*t* 3 d, >99%, dr 95:5) to **6s**. ^{1}H-NMR (400 MHz, C_6D_6): 7.47 (*d*, *J* = 7.2, 2 H); 7.41–7.39 (*m*, 2 H); 7.20–7.09 (*m*, 6); 6.09 (*s*, 1 H); 4.64–4.54 (*m*, 1 H); 4.15 (*t*, *J* = 6.4, 1 H); 3.94 (*q*, *J* = 6.8, 1 H); 3.40 (*d*, *J* = 11.2, 1 H); 2.73–2.64 (*m*, 2 H); 2.19–2.11 (*m*, 1 H); 1.75–1.66 (*m*, 3 H); 1.61–1.55 (*m*, 1 H); 1.30–1.26 (*m*, 1 H); 1.13–1.06 (*m*, 1 H); 1.03 (*d*, *J* = 6.8, 3 H); 0.94 (*t*, *J* = 6.8, 3 H); 0.88 (*t*, *J* = 7.2, 3 H); 0.66–0.58 (*m*, 1 H); −0.13 (*s*, 9 H). ^{13}C-NMR (100 MHz, C_6D_6): 172.9; 143.4; 142.3; 140.1; 130.2; 129.8; 127.5; 127.3; 106.5; 83.9; 73.2; 60.9; 54.1; 53.7; 34.4; 27.6; 24.6; 23.5; 18.3; 14.8; 14.1; 2.1.

6.2. *Conversion of* **6r** *to Oxazine* **5b**. To the soln. of **6r** (30.7 mg, 0.058 mmol) in (D_8)toluene (0.6 ml) in the presence of MS (3 Å) in an NMR tube was added 4-nitrophenol (3.2 mg, 40 mol-%), and the reaction was monitored by ^{1}H-NMR. The oxazine *N*-oxide **5b** was slowly formed at r.t. (24 h, 30% conversion). For NMR data *vide supra*, *Exper. Part*, *Sect. 5*. We assume that the resulting ratio **6r**/**5b** 7:3 is a thermodynamic ratio.

6.3. *Deuterium Labeling of* **6a**. To a C_6D_6 soln. (0.6 ml) of **1a** (32.6 mg, 0.1 mmol) in an NMR tube were added 3-Å MS (3 mm high) and [2,2-D_2]propanal (7.5 µl, 0.1 mmol) at rt, the mixture was agitated and allowed to stand for 15 min. The ^{1}H-NMR spectrum was recorded to check the H/D ratio. β-Nitrostyrene (14.9 mg, 0.1 mmol) was then added to the NMR tube, and formation of cyclobutane and oxazine was confirmed by ^{1}H-NMR. After keeping the NMR tube for 20 h at r.t., H/D ratio in the α-position to the NO_2 group of **6a** was determined by ^{1}H-NMR as 26% D incorporation (*Scheme 6*, *b*).

6.4. *Diastereoselectivity of the Hydrolysis of* **6a** *to Nitro Aldehyde* **7a**. To a benzene soln. (8 ml) of **6a** (257 mg, 0.5 mmol) were added H_2O (9 mg, 0.5 mmol) in benzene (2 ml) and 4-nitrophenol (69.5 mg, 0.5 mmol) at r. t. The mixture was stirred at r.t., and aliquots were taken for ^{1}H-NMR recordings to check the diastereoisomer ratio of *Michael* product **7a** at 15 min, 30 min, 1.5 h, 16 h, and 40 h. The results are compiled in *Scheme 7*.

7. *Reaction of the* Michael *Adduct* **8** *of* **1a** *with* tert-*Butyl 3-Nitroacrylate*. 7.1. *Formation of* **8** *in* C_6D_6 *or in* CD_2Cl_2. tert-*Butyl (2*R*)-2-[(2*S*)-2-{Diphenyl[(trimethylsilyl)oxy]methyl}pyrrolidin-1-yl]-3-nitropropanoate* (**8**). To a soln. of *tert*-butyl (*E*)-3-nitroacrylate (8.7 mg, 0.05 mmol) in C_6D_6 (0.6 ml) or in CD_2Cl_2 (0.6 ml) in an NMR tube, **1a** (16.3 mg, 0.05 mmol) was added, the mixture was agitated, and the reaction was monitored by ^{1}H-NMR. The adduct **8** was formed (in C_6D_6: *t* 30 min, >99% conversion, dr 1.5:1; in CD_2Cl_2: *t* 10 min, >99% conversion, dr 1:1). ^{1}H-NMR (400 MHz, C_6D_6): Major diastereoisomer: 7.63–7.61 (*m*, 2 H); 7.52–7.47 (*m*, 2 H); 7.18–7.04 (*m*, 6 H); 4.88 (*t*, *J* = 7.2, 1 H); 4.78 (*dd*, *J* = 2.4, 9.6, 1 H); 4.40 (*dd*, *J* = 8.8, 13.2, 1 H); 4.13–4.05 (*m*, 1 H); 2.50–2.44 (*m*, 1 H); 2.42–2.32 (*m*, 1 H); 1.99–1.89 (*m*, 1 H); 1.79–1.74 (*m*, 1 H); 1.31 (*s*, 9 H); 1.21–1.14 (*m*, 1 H); 0.59–0.51 (*m*, 1 H); −0.07 (*s*, 9 H); minor diastereoisomer: 7.63–7.61 (*m*, 2 H); 7.52–7.47 (*m*, 2 H); 7.18–7.04 (*m*, 6 H); 4.80–4.74 (*m*, 1 H); 4.62 (*dd*, *J* = 8.8, 10.0, 1 H); 4.13–4.05 (*m*, 1 H); 3.93 (*dd*, *J* = 3.2, 9.2, 1 H); 2.42–2.32 (*m*, 1 H); 2.26–2.20 (*m*, 1 H); 1.65–1.54 (*m*, 2 H); 1.37 (*s*, 9 H); 0.98–0.89 (*m*, 1 H); 0.36–0.24 (*m*, 1 H); −0.06 (*s*, 9 H).

7.2. *Reaction between Adduct* **8** *and Isovaleraldehyde* (= *3-Methylbutanal*). To a soln. of **8** (24.9 mg, 0.05 mmol) in C_6D_6 (0.6 ml) or in CD_2Cl_2 (0.6 ml) in an NMR tube isovaleraldehyde (5.4 µl, 0.05 mmol) was added, the reaction was monitored by ^{1}H-NMR to follow the formation of **4g**, **6g**, and **7g**. The results are collected in *Table 7*. For NMR data of **4g** and **6g**, *vide* supra, *Sect. 3* and *6* in the *Exper. Part*, resp.

Table 7. *Reaction of* **8** *with 3-Methylbutanal.* Ratios determined by NMR-peak integration of the products **4g**, **6g**, and **7g**.

Solvent	Time [h]	**8** [%]	**4g** [%]	**6g** [%]	**7g** [%]
CD_2Cl_2	1	81	19		
	18	7	12	23	58 (dr 4:1)
	72			28	72 (dr 1.6:1)
(D_6)benzene	19	63	37		
	96	33	15	7	45 (dr 1.4:1)

tert-*Butyl (2*R*)-3-Formyl-4-methyl-2-(nitromethyl)pentanoate* (**7g**). ^{1}H-NMR (300 MHz, CD_2Cl_2) 9.79 (*d*, *J* = 1.5, 1 H); 4.80 (*dd*, *J* = 10.5, 14.4, 1 H); 4.35 (*dd*, *J* = 3.3, 14.7, 1 H); 3.56 – 3.49 (*m*, 1 H); 2.82 – 2.76 (*m*, 1 H); 1.64 – 1.60 (*m*, 1 H); 1.44 (*s*, 9 H); 0.97 (*d*, *J* = 6.0, 6 H).

8. *Intermediates* **13** *and* **14** *in Tripeptide-Catalyzed* Michael *Additions. Methyl (4*S*)-4-({[(2*S*)-1-({(2*R*)-1-[(1*R*,2*S*,3*R*,4*R*)-3-(*tert*-Butyl)-2-isopropyl-4-nitrocyclobutyl]pyrrolidin-2-yl}carbonyl)pyrrolidin-2-yl]carbonyl}amino)-5-(dodecylamino)-5-oxopentanoate* (**13**). To a soln. of **11c** [19] (26 mg, 0.05 mmol) in C_6D_6 (0.6 ml) with MS (4 Å) in an NMR tube, isovaleraldehyde (5.4 µl, 0.05 mmol) was added, the mixture was agitated, and the reaction was monitored by ^{1}H-NMR to follow the enamine formation. When **12b** had been formed, (*E*)-3,3-dimethyl-1-nitrobut-1-ene (6.5 mg, 0.05mmol) was added, and the mixture was agitated at r.t., and then the reaction was monitored by ^{1}H-NMR to detect the formation of cyclobutane **13** (*t* 20 h). Purification by prep. TLC (AcOEt) afforded **13** (19 mg, 52%). ^{1}H-NMR (600 MHz, C_6D_6): 7.22 (*d*, *J* = 7.8, 1 H); 6.98 (*t*, *J* = 4.8, 1 H); 4.71 – 4.67 (*m*, 2 H); 4.43 (*dd*, *J* = 4.2, 7.2, 1 H); 3.91 (*dd*, *J* = 7.2, 9.0, 1 H); 3.59 – 3.53 (*m*, 2 H); 3.36 (*s*, 3 H); 3.35 – 3.31 (*m*, 1 H); 3.19 – 3.14 (*m*, 1 H); 2.93 (*td*, *J* = 3.6, 7.8, 1 H); 2.88 – 2.84 (*m*, 1 H); 2.52 – 2.46 (*m*, 2 H); 2.42 – 2.39 (*m*, 2 H); 2.37 – 2.33 (*m*, 1 H); 2.26 – 2.19 (*m*, 1 H); 2.01 – 1.98 (*m*, 1 H); 1.85 – 1.79 (*m*, 2 H); 1.74 – 1.66 (*m*, 2 H); 1.63 – 1.55 (*m*, 3 H); 1.50 – 1.45 (*m*, 1 H); 1.39 – 1.21 (*m*, 21 H); 1.13 (*d*, *J* = 6.6, 3 H); 1.10 (*d*, *J* = 6.6, 3 H); 0.92 (*t*, *J* = 7.2, 3 H); 0.76 (*s*, 9 H); ^{13}C-NMR (100 MHz, C_6D_6): 174.1; 172.7; 171.4; 170.8; 78.2; 62.0; 61.8; 60.5; 54.0; 51.3; 48.4; 47.1; 47.0; 41.9; 40.0; 32.4; 31.8; 31.0; 30.2; 30.2; 30.1; 30.1; 30.0; 29.9; 29.9; 29.0; 28.9; 27.4; 27.4; 27.4; 25.0; 23.3; 23.2; 21.3; 18.5; 14.4. HR-ESI-MS: 720.5269 ($[M+H]^+$, $C_{39}H_{70}N_5O_7^+$; calc. 720.5270 (err., 0.1 ppm)).

*Methyl (4*S*)-4-({[(2*S*)-1-({(2*R*)-1-[(4*R*,5*S*,6*S*)-3,5-Dimethyl-2-oxido-4-phenyl-5,6-dihydro-4*H*-1,2-oxazin-6-yl]pyrrolidin-2-yl}carbonyl)pyrrolidin-2-yl]carbonyl}amino)-5-(dodecylamino)-5-oxopentanoate* (**14a**). To a soln. of **11c** [19] (20 mg, 0.038 mmol) in C_6D_6 (0.6 ml) with MS (4 Å) in an NMR tube was added propanal (2.7 µl, 0.038 mmol) was added, the mixture was agitated, and the reaction was monitored by ^{1}H-NMR to follow the enamine formation. When enamine formation was complete, (*E*)-*β*-methyl-*β*-nitrostyrene (6.2 mg, 0.038) was added, and the mixture was agitated at r.t., and then the reaction was monitored by ^{1}H-NMR; **14a** was formed with complete conversion within 10 min. Purification failed due to decomposition. ^{1}H-NMR (400 MHz, C_6D_6): 7.57 (*d*, *J* = 8.0, 1 H); 7.12 – 6.97 (*m*, 5 H); 6.84 – 6.82 (*m*, 1 H); 5.27 (*d*, *J* = 10.0, 1 H); 4.72 – 4.67 (*m*, 1 H); 4.47 (*dd*, *J* = 3.6, 8.4, 1 H); 4.31 (*t*, *J* = 6.8, 1 H); 3.74 – 3.69 (*m*, 1 H); 3.50 – 3.44 (*m*, 1 H); 3.40 (*s*, 3 H); 3.39 – 3.35 (*m*, 1 H); 3.21 – 3.11 (*m*, 1 H); 3.05 – 3.00 (*m*, 1 H); 2.94 – 2.83 (*m*, 2 H); 2.52 – 2.44 (*m*, 1 H); 2.40 – 2.30 (*m*, 2 H); 2.20 – 2.11 (*m*, 2 H); 2.00 – 1.93 (*m*, 1 H); 1.80 (*d*, *J* = 0.8, 3 H); 1.71 – 1.52 (*m*, 6 H); 1.36 – 1.20 (*m*, 21 H); 1.14 (*d*, *J* = 6.4, 3 H); 0.91 (*t*, *J* = 6.8, 3 H). ^{13}C-NMR (100 MHz, C_6D_6): 174.5; 172.7; 172.1; 171.1; 141.3; 130.1; 129.6; 129.2; 128.8; 127.6; 122.1; 97.0; 61.7; 60.8; 53.9; 53.5; 51.6; 47.2; 43.7; 41.5; 40.1; 32.4; 30.8; 30.2; 30.2; 30.1; 30.0; 29.9; 29.3; 29.1; 27.7; 27.5; 25.1; 24.4; 23.2; 17.4; 14.8; 14.4.

*Methyl (4*S*)-5-(Dodecylamino)-4-({[(2*S*)-1-({(2*R*)-1-[(4*R*,5*S*,6*S*)-3-methyl-2-oxido-4-phenyl-5-(propan-2-yl)-5,6-dihydro-4*H*-1,2-oxazin-6-yl]pyrrolidin-2-yl}carbonyl)pyrrolidin-2-yl]carbonyl}amino)-5-oxopentanoate* (**14b**) *and Methyl (4*S*)-5-(Dodecylamino)-4-({[(2*S*)-1-({(2*R*)-1-[(1*R*,2*R*,3*R*,4*S*)-2-methyl-2-nitro-3-phenyl-4-(propan-2-yl)cyclobutyl]pyrrolidin-2-yl}carbonyl)pyrrolidin-2-yl]carbonyl}amino)-5-oxopentanoate* (**14c**). To a soln. of **11c** [19] (22 mg, 0.042 mmol) in C_6D_6 (0.6 ml) with MS (3 Å) in an NMR tube, isovaleraldehyde (4.6 µl, 0.042 mmol) was added, the mixture was agitated, and the reaction was monitored by ^{1}H-NMR to follow the enamine formation. When **12b** had been formed, (*E*)-*β*-methyl-*β*-nitrostyrene (6.8 mg, 0.042 mmol) was added, and the mixture was agitated at r.t., and then the reaction was monitored by ^{1}H-NMR; **14b** and **14c** were formed in 2 h (conversion > 85%). The two compounds were identified and characterized by 1D- and 2D-NMR (COSY, HSQC, HMBC, and NOESY). The equilibration between **14b** and **14c** 1 : 1.5 was detected by an EXSY spectrum. Measurement of temp.-dependent equilibrium between **14b** and **14c**, and the corresponding enamine **12b** and nitro olefin: ^{1}H-NMR (300 MHz, C_6D_6) at r.t.: **12b/14b/14c** 1 : 7 : 10.5; at 50°, **12b/14b/14c** 1 : 1.5 : 2.5; cooling the sample back to r.t., after further 2 h, **12b/14b/14c** 1 : 7 : 10.5. Purification failed due to decomposition.

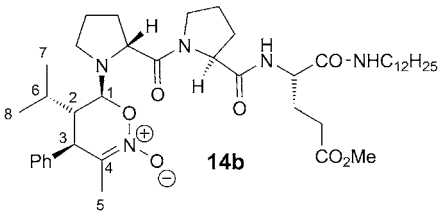
Data of **14b**: ^{1}H-NMR (400 MHz, C_6D_6): 7.53 (*d*, *J* = 7.2, 1 H); 7.34 (*d*, *J* = 8.0, 1 H); 7.23 – 6.97 (*m*, 4 H); 6.95 – 6.93 (*m*, 1 H); 5.36 (*d*, *J* = 9.6, 1 H); 4.73 – 4.64 (*m*, 1 H); 4.50 – 4.46 (*m*, 1 H); 4.36 – 4.32 (*m*,

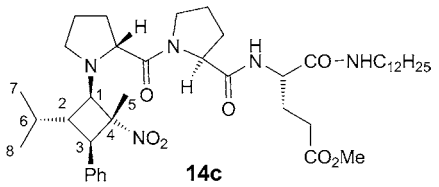
1 H); 3.50 – 3.41 (*m*, 1 H); 3.44 (*s*, 3 H); 3.40 – 2.82 (*m*, 7 H); 2.58 – 1.98 (*m*, 5 H); 1.81 (*s*, 3 H); 1.72 – 1.50 (*m*, 6 H); 1.35 – 1.21 (*m*, 22 H); 1.15 (*d*, *J* = 7.2, 3 H); 0.95 (*d*, *J* = 7.2, 3 H); 0.91 (*t*, *J* = 6.8, 3 H).

Data of **14c**: 7.39 (*d*, *J* = 7.2, 2 H); 7.26 – 6.82 (*m*, 5 H); 4.82 – 4.76 (*m*, 1 H); 4.61 (*dd*, *J* = 3.2, 8.4, 1 H); 4.27 (*d*, *J* = 8.8, 1 H); 4.07 (*d*, *J* = 10.8, 1 H); 4.05 – 4.01 (*m*, 1 H); 3.80 – 3.73 (*m*, 1 H); 3.38 (*s*, 3 H); 3.40 – 2.82 (*m*, 6 H); 2.58 – 1.98 (*m*, 5 H); 1.72 – 1.50 (*m*, 6 H); 1.35 – 1.21 (*m*, 22 H); 1.15 (*s*, 3 H); 1.12 (*d*, *J* = 6.8, 3 H); 0.99 (*d*, *J* = 6.8, 3 H); 0.91 (*t*, *J* = 6.8, 3 H).

The most characteristic NMR chemical shifts of **14b** and **14c** are given in *Table 8*. **14c**: HMBC (400 MHz, C_6D_6): C(1)/H(5), C(3)/H(5), C(4)/H(1), C(4)/H(3), C(4)/H(5). NOESY (600 MHz, C_6D_6): H(2)/H(5), H(1)/H(6), H(1)/H(7), H(1)/H(8), H(3)/H(6), H(3)/H(7), H(3)/H(8). For atom numbering, see *Table 8*.

Table 8. *Comparison of Characteristic NMR Chemical Shifts of* **14b** *and* **14c**





Position	**14b**		**14c**	
	δ(H) [ppm]	δ(C) [ppm]	δ(H) [ppm]	δ(C) [ppm]
1	5.36 (*d*, *J* = 9.6)	96.3	4.27 (*d*, *J* = 8.8)	62.1
2	2.48 (*m*)	51.8	2.25 (*m*)	42.7
3	3.41 (*m*)	47.9	4.07 (*d*, *J* = 10.8)	47.2
4		123.1		91.7
5	1.81 (*s*)	16.9	1.15 (*s*)	17.4

9. *Reactions with OH-Substituted Nitro Olefins* **15** *and* **19**. *(2*S*)-2-{Diphenyl[(trimethylsilyl)oxy]-methyl}-1-[(2*R*,3*R*,4*S*)-3,4-dihydro-3-isopropyl-4-(nitromethyl)-2*H*-chromen-2-yl]pyrrolidine* (**21**). Prepared according to *GP* from **1a** (32.6 mg, 0.1 mmol), isovaleraldehyde (10.8 µl, 0.1 mmol), and *(*E*)-2-(2-nitroethenyl)phenol* (**19**; 16.5 mg, 0.1 mmol; *t* 10 min). After completion of the reaction (monitoring by ^{1}H-NMR), the soln. was filtered and concentrated to afford the crude product. Crystallization from hexane yielded **21** (25 mg, 45%). Pale-yellow crystals, suitable for X-ray analysis. M.p. 101 – 102° (dec). ^{1}H-NMR (400 MHz, C_6D_6): 7.55 (*d*, *J* = 7.2, 2 H); 7.48 – 7.46 (*m*, 2 H); 7.20 – 6.94 (*m*, 9 H); 6.67 (*td*, *J* = 1.2, 7.2, 1 H); 4.90 (*d*, *J* = 10.8, 1 H); 4.83 (*dd*, *J* = 3.2, 9.2, 1 H); 4.15 (*d*, *J* = 7.2, 2 H); 3.60 (*td*, *J* = 3.6, 7.2, 1 H); 2.52 (*q*, *J* = 9.2, 1 H); 2.19 – 2.10 (*m*, 2 H); 2.05 – 2.00 (*m*, 1 H); 1.58 – 1.53 (*m*, 1 H); 1.41 – 1.29 (*m*, 2 H); 0.84 (*d*, *J* = 6.8, 3 H); 0.62 – 0.69 (*m*, 1 H); 0.50 (*d*, *J* = 5.6, 3 H); – 0.07 (*s*, 9 H). ^{13}C-NMR (100 MHz, C_6D_6): 156.0; 144.4; 144.0; 130.2; 129.8; 129.6; 128.4; 128.2; 127.9; 127.7; 127.4; 127.3; 124.8; 120.4; 116.6; 93.4; 84.8; 77.4; 69.7; 46.5; 44.5; 37.7; 29.7; 27.8; 24.8; 22.2; 19.6; 2.3. HR-ESI-MS: 559.2987 ($[M+H]^+$, $C_{33}H_{43}N_2O_4Si^+$; calc. 559.2987 (err., 0.0 ppm)).

*(2*S*)-2-{Diphenyl[(trimethylsilyl)oxy]methyl}-1-[(2*R*,3*R*,4*S*,5*S*)-5-nitro-4-phenyl-3-propyltetrahydro-2*H*-pyran-2-yl]pyrrolidine* (**22a**). Prepared according to *GP* from **1a** (32.6 mg, 0.1 mmol), valeraldehyde (10.8 µl, 0.1 mmol), and **15** (17.9 mg, 0.1 mmol; *t* 10 min). FC (hexane/EA 10 : 1) afforded **22a** (44 mg, 77%). Colorless solid. M.p. 145 – 146° (dec). R_f(hexane/AcOEt 10 : 1) 0.43. $[\alpha]^{23}_D = -141.7$ ($c = 0.50$, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.58 – 7.56 (*m*, 2 H); 7.54 – 7.51 (*m*, 2 H); 7.35 – 7.26 (*m*, 9 H); 7.19 – 7.16 (*m*, 2 H); 4.77 (*td*, *J* = 4.8, 10.8, 1 H); 4.51 (*dd*, *J* = 3.2, 8.8, 1 H); 4.43 (*dd*, *J* = 4.8, 10.8, 2 H); 3.82 (*t*, *J* = 10.4, 1 H); 3.14 (*t*, *J* = 11.6, 1 H); 2.94 – 2.87 (*m*, 1 H); 2.36 (*td*, *J* = 2.4, 8.4, 1 H); 1.95 – 1.84 (*m*, 3 H); 1.36 – 1.18 (*m*, 3 H); 1.02 – 0.87 (*m*, 2 H); 0.61(*t*, *J* = 7.2, 3 H); 0.38 – 0.27 (*m*, 1 H); – 0.14 (*s*, 9 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 143.7; 137.8; 130.0; 129.9; 129.0; 128.0; 127.9; 127.5; 127.3; 127.2;

Table 9. *Experimental Details for the X-Ray Structures of* **4q**, **5b**, **5c**, **5d**, **21**, *and* **23**

	4q	**5b**	**5c**	**5d**	**21**	**23**
CCDC No. [a])	883666	883668	919662	883667	919664	919663
Chemical formula	$C_{31}H_{46}N_2O_3Si$	$C_{32}H_{40}N_2O_3Si$	$C_{34}H_{44}N_2O_3Si$	$C_{34}H_{44}N_2O_3Si$	$C_{33}H_{42}N_2O_4Si$	$C_{31}H_{36}N_2O_4$
M_r [g/mol]	522.79	528.75	556.80	556.80	558.78	500.62
Crystal size [mm]	0.20 x 0.12 x 0.03 mm	0.18 x 0.16 x 0.12 mm	0.12 x 0.08 x 0.04 mm	0.26 x 0.18 x 0.16 mm	0.28 x 0.22 x 0.20 mm	0.20 x 0.18 x 0.02 mm
Space group	$P2_12_12_1$	$P2_1$	$P2_1$	$P2_1$	$P2_12_12_1$	$C2$
Crystal shape	Orthorhombic	Monoclinic	Monoclinic	Monoclinic	Orthorhombic	Monoclinic
a [Å]	10.4899(6)	9.5550(3)	9.6978(9)	10.4708(4)	9.1983(3)	23.940(2)
b [Å]	14.9108(6)	10.7941(3)	10.5115(9)	14.1448(6)	15.0166(5)	7.1220(6)
c [Å]	19.2209(10)	14.6652(4)	15.0807(13)	10.6950(5)	21.6324(7)	15.3957(13)
α [°]	90.00	90.00	90.00	90.00	90.00	90.00
β [°]	90.00	92.0530(10)	90.194(6)	98.722(2)	90.00	95.976(7)
γ [°]	90.00	90	90.00	90.00	90.00	90.00
V [Å^3]	3006.4(3)	1511.56(8)	1537.3(2)	1565.69(12)	2988.02(17)	2610.7(4)
Z	4	2	2	2	4	4
ϱ_{calc} [g · cm^{-3}]	1.155	1.162	1.203	1.181	1.242	1.274
μ [mm^{-1}]	0.111	0.111	0.113	0.111	0.118	0.084
Temp. [K]	100(2)	100(2)	100(2)	100(2)	100(2)	100(2)
θ_{max} [°]	27.52	27.51	27.58	27.63	27.65	27.58
Reflections:						
independent	6908	5576	6311	7206	6806	5523
observed ($I > 2\sigma$)	5851	5165	4090	5822	6104	4637
Variables	519	490	537	396	529	478
R(all)	0.0547	0.0332	0.1038	0.0634	0.0439	0.0514
R(gt)	0.0412	0.0284	0.0544	0.0449	0.0356	0.0367
Flack	− 0.2(1)	0.0(1)	0.1(2)	− 0.0(1)	− 0.0(1)	− 0.5(8)
Δ/σ_{max}	0.005	0.002	0.001	0.018	0.001	0.001
$\Delta\varrho_{max}$ [e Å^{-3}]	0.267	0.228	0.443	0.275	0.523	0.257

[a]) Copies of the data can be obtained, free of charge, on application to the *Cambridge Crystallographic Data Centre* (*CCDC*), 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

127.1; 95.6; 88.6; 84.2; 68.3; 68.1; 50.4; 46.4; 43.4; 29.9; 28.9; 24.1; 14.7; 2.3. HR-ESI-MS: 573.3141 ([M+H]$^+$, $C_{34}H_{45}N_2O_4Si^+$; calc. 573.3143 (err., 0.4 ppm)).

*(2*S*)-2-{Diphenyl[(trimethylsilyl)oxy]methyl}-1-[(2*R*,3*R*,4*S*,5*S*)-3-isopropyl-5-nitro-4-phenyltetrahydro-2*H*-pyran-2-yl]pyrrolidine* (**22b**). Prepared according to *GP* from **1a** (32.5 mg, 0.1 mmol), isovaleraldehyde (10.8 µl, 0.1 mmol), and **15** (17.9 mg, 0.1 mmol; *t* 10 min). FC (hexane/AcOEt 10:1) afforded **22b** (38 mg, 66%). Colorless solid. M.p. 79–80° (dec). R_f(hexane/AcOEt 10:1) 0.50. $[\alpha]^{22}_D$ = −131.7 (c = 1.90, $CHCl_3$). IR (neat): 2931*w*, 2955*w*, 1736*w*, 1602*w*, 1548*m*, 1493*w*, 1448*w*, 1382*w*, 1344*w*, 1250*m*, 1215*w*, 1136*w*, 1087*m*, 1061*m*, 908*m*, 898*m*, 878*m*, 836*s*, 732*s*, 700*s*. ^{1}H-NMR (600 MHz, $CDCl_3$): 7.76 (*m*, 4 H); 7.31–7.30 (*m*, 6 H); 7.25–7.28 (*m*, 2 H); 7.23–7.21 (*m*, 1 H); 7.18 (*d*, *J* = 7.8, 2 H); 4.74 (*td*, *J* = 4.8, 10.8, 1 H); 4.53 (*m*, 1 H); 4.45 (br. *s*, 1 H); 4.37 (*dd*, *J* = 6.0, 10.2, 1 H); 3.77 (*t*, *J* = 10.8, 1 H); 3.25 (*t*, *J* = 10.8, 1 H); 2.85 (*q*, *J* = 10.8, 1 H); 2.32 (*t*, *J* = 6.6, 1 H); 2.07 (br. *s*, 1 H); 1.91 (*t*, *J* = 10.8, 1 H); 1.87–1.85 (*m*, 2 H); 1.32–1.27 (*m*, 1 H); 0.61 (br. *s*, 3 H); 0.41–0.32 (*m*, 1 H); 0.21 (*d*, *J* = 6.0, 3 H); −0.17 (*s*, 9 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 143.8; 138.8; 130.0; 129.9; 128.8; 127.8; 127.3; 127.2; 127.1; 95.0; 89.6; 84.6; 68.0; 67.8; 48.4; 47.9; 46.4; 29.9; 26.7; 24.0; 22.2; 17.3; 2.3. HR-ESI-MS: 573.3138 ([M+H]$^+$, $C_{34}H_{45}N_2O_4Si^+$; calc. 573.3143 (err., 0.9 ppm)).

*{(2*S*)-1-[(2*R*,3*R*,4*S*,5*S*)-Tetrahydro-3-isopropyl-5-nitro-4-phenyl-2*H*-pyran-2-yl]pyrrolidin-2-yl}(diphenyl)methanol* (**23**). To a soln. of **22b** (27 mg, 0.047 mmol) in EtOH (0.5 ml) HCl (10%, 0.5 ml) was added. The mixture was stirred at r.t., and the reaction was monitored by TLC. After 1 h, the reaction was complete. After addition of AcOEt the soln. was dried (Na_2SO_4) and concentrated. FC (hexane/AcOEt 4:1) afforded **23** (19 mg, 81%). Recrystallization from hexane/Et_2O yielded colorless crystals, suitable for X-ray analysis. M.p. 170–171°. R_f(Hexane/AcOEt 4:1) 0.56. $[\alpha]^{23}_D$ = −83.6 (c = 0.64, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.76 (*d*, *J* = 7.2, 2 H); 7.58 (*d*, *J* = 7.2, 2 H); 7.37 (*t*, *J* = 7.2, 2 H); 7.31–7.24 (*m*, 7 H); 7.15 (*t*, *J* = 6.8, 2 H); 4.78–4.75 (*m*, 1 H); 4.71 (*dt*, *J* = 4.8, 10.8, 1 H); 4.28 (*dd*, *J* = 4.8, 10.8, 1 H); 4.13 (*s*, 1 H); 3.66 (*d*, *J* = 9.6, 1 H); 3.34 (*t*, *J* = 10.4, 1 H); 3.23–3.17 (*m*, 1 H); 2.99–2.93 (*m*, 1 H); 2.96 (*t*, *J* = 11.2, 1 H); 1.96 (*t*, *J* = 10.4, 1 H); 1.92–1.84 (*m*, 1 H); 1.78–1.67 (*m*, 4 H); 0.62 (*d*, *J* = 7.2, 3 H); 0.25 (*d*, *J* = 7.2, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 148.0; 146.6; 138.3; 128.9; 128.5;128.2; 128.0; 127.0; 126.4; 125.7; 125.2; 91.3; 88.9; 67.5; 65.4; 48.1; 47.7; 47.2; 29.6; 27.1; 24.7; 20.9; 18.3. HR-ESI-MS: 501.2752 ([M+H]$^+$, $C_{31}H_{37}N_2O_4^+$; calc. 501.2748 (err., −0.8 ppm)).

*(2*R*,3*R*,4*S*,5*S*)-Tetrahydro-5-nitro-4-phenyl-3-propyl-2*H*-pyran-2-ol* (**16**). To a soln. of **22a** (18 mg, 0.031 mmol) in THF (0.2 ml), 3-nitrobenzoic acid (12.5 mg, 0.075 mmol) and H_2O (5.6 mg, 0.31 mmol) were added. The mixture was stirred at r.t. for 48 h, and then diluted with AcOEt, dried (Na_2SO_4), and concentrated. FC (hexane/AcOEt 4:1) afforded **16** (7 mg, 78%). R_f(hexane/AcOEt 4:1) 0.33. $[\alpha]^{22}_D$ = +13.3 (c = 0.26, MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 7.33–7.28 (*m*, 3 H); 7.20–7.17 (*m*, 2 H); 5.32 (*t*, *J* = 3.3, 1 H); 4.88 (*td*, *J* = 5.1, 11.4, 1 H); 4.43 (*t*, *J* = 10.5, 1 H); 4.03 (*dd*, *J* = 5.1, 10.5, 1 H); 3.52 (*t*, *J* = 11.7, 1 H); 2.52 (*dd*, *J* = 1.5, 3.3, 1 H); 2.05–1.96 (*m*, 1 H); 1.40–1.25 (*m*, 2 H); 1.17–1.03 (*m*, 1 H); 0.98–0.88 (*m*, 1 H); 0.75 (*t*, *J* = 6.9, 3 H). HR-ESI-MS: 288.1210 ([M+Na]$^+$, $C_{14}H_{19}N_1Na_1O_4^+$; calc. 288.1206 (err., −1.4 ppm)). Data are in agreement with those in [27].

10. *Determination of the X-Ray Structures* (*Table 9*). All structures were determined by the X-ray service unit of the Laboratorium für Organische Chemie, ETH-Zürich. Suitable single crystals were analyzed on *Bruker Nonius Apex-II* (for **4q**, **5d** and **21**) or *Bruker Kappa Apex-II Duo* (for **5b**, **5c** and **23**) CCD diffractometers with MoK_α radiation (λ 0.71073 Å, graphite monochromator). Structures were solved by direct methods with SHELXL97 [53] and refined by full-matrix least-squares on F^2 (SHELXL97) [53]. If possible, the H-atoms were located from a difference electron-density map and refined isotropically or constrained at ideal positions and included in the structure factor calculation. The absolute configurations are determined by X-ray analyses or derived from the known sense of chirality of the chiral auxiliary (for **23**).

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