# Are Oxazolidinones Really Unproductive, Parasitic Species in Proline Catalysis? – Thoughts and Experiments Pointing to an Alternative View

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and

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Dedicated to Professor *Yoshito Kishi* on the occasion of his 70th birthday

The N,O-acetal and N,O-ketal derivatives (oxazolidinones) formed from proline, and aldehydes or ketones are well-known today, and they are detectable in reaction mixtures involving proline catalysis, where they have been considered 'parasitic dead ends'. We disclose results of experiments performed in the early 1970's, and we describe more recent findings about the isolation, characterization, and reactions of the oxazolidinone derived from proline and cyclohexanone. This oxazolidinone reacts (THF, room temperature) with the electrophiles $\beta$-nitrostyrene and chloral (=trichloroacetaldehyde), to give the *Michael* and aldol adduct, respectively, after aqueous workup (*Scheme 5*). The reactions occur even at $-75°$ when catalyzed with bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or EtN(i-Pr)$_2$ (DIPEA) (10%; *Table 1*). It is shown by NMR (*Figs. 1* and *3*) and IR analysis (*Figs. 2* and *4*) that the primarily detectable product (before hydrolysis) of the reaction with the nitro-olefin is again an oxazolidinone. When dissolved in hydroxylic solvents such as MeOH, 'hexafluoroisopropanol' ((CF$_3$)$_2$CHOH; HFIP), AcOH, CF$_3$COOH, or in LiBr-saturated THF, the ring of the oxazolidinone from cyclohexanone and proline opens up to the corresponding iminium ion (*Tables 2–4*), and when treated with strong bases such as DBU (in (D$_8$)THF) the enamino-carboxylate derived from proline and cyclohexanone is formed (*Scheme 8*). Thus, the two hitherto putative participants (iminium ion and enamine) of the catalytic cycle (*Scheme 9*) have been characterized for the first time. The commonly accepted mechanism of the stereoselective C,C- or C,X-bond-forming step (*i.e.*, **A**–**D**) of this cycle is discussed and challenged by thoughts about an alternative model with a pivotal role of oxazolidinones in the regio- and diastereoselective formation of the intermediate enamino acid (by elimination) and in the subsequent reaction with an electrophile (by *trans*-addition with lactonization; *Schemes 11–14*). The stereochemical bias between *endo*- and *exo*-space of the bicyclo[3.3.0]octane-type oxazolidinone structure (*Figs. 5* and *6*) is considered to possibly be decisive for the stereochemical course of events.

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[3]) Part of the results described herein have been mentioned in a published lecture by *A. E.* in 1976 [1].

[4]) Postdoctoral Research Associate with *A. E.*, ETH-Zürich, report of December 1975.

[5]) Part of the Ph.D. thesis by *R. H.*, ETH-Zürich 1977 [2a].

Finally, the remarkable consistency, with which the diastereotopic *Re*-face of the double bond of pyrrolidino-enamines (derived from proline) is attacked by electrophiles (*Schemes 1* and *15*), and the likewise consistent reversal to the *Si*-face with bulky $(Aryl)_2C$-substituents on the pyrrolidine ring (*Scheme 16*) are discussed by invoking stereoelectronic assistance from the lone pair of pyramidalized enamine N-atoms.

**1. Introduction.** – We would hardly have considered to become engaged in the timely research area of '*organocatalysis*', had not, in the recent literature, the name of one of the present authors (*D. S.*) been implied in a statement on the mechanism of the stereoselection in proline catalysis (see title) such that this author was incited to think that this statement may require further scrutiny. The assignment of the role of '*unproductive parasitic species*' to oxazolidinones [3] presumably has its roots in chemical reasoning according to which either enamine carboxylic acids or their carboxylates of type **1** *must* constitute the nucleophilic species reacting in proline-catalyzed reactions of aldehydes or ketones with electrophiles [3] (*Scheme 1*)[6]), even though such intermediates have not been detected by NMR spectroscopy in any of a variety of solvents [5], quite in contrast to corresponding oxazolidinones of type **2**, which are seen spectroscopically whenever aldehydes or ketones, and proline are mixed in solvents such as DMSO in the presence of molecular sieves. The greater stability of oxazolidinones[7]) relative to their enamine carboxylic acid isomers is not surprising, while observations such as those of *Orsini et al.* [7] according to which the stability of oxazolidinones derived from aldehydes and proline decreases from chloral (=trichloroacetaldehyde) to pivalaldehyde (=2,2-dimethylpropanal) to $\alpha$-branched aldehydes (*cf.* 2-methylpropanal) to aldehydes without $\alpha$-branching (*cf.* 3-methylbutanal)[8]), deserve our attention. More recently the groups of *List et al.* [5], and *Blackmond* and co-workers [8] have reported NMR detections of oxazolidinones **2** derived from both aldehydes and ketones in reaction mixtures of proline-catalyzed processes.

Early work on oxazolidinones in the context of studies on the mechanism of stereoselection in proline-catalyzed aldolizations dates back at ETH to the early 1970's, when oxazolidinones derived from pivalaldehyde and cyclohexanone were prepared and studied, apparently for the first time in this thematic context[9])[2]. Due to the failure of reaching a consistent mechanistic conclusion from conflicting and inconclusive experimental observations made in extended model studies carried out at that time, that work remained unpublished, with the exception of two joint papers of the

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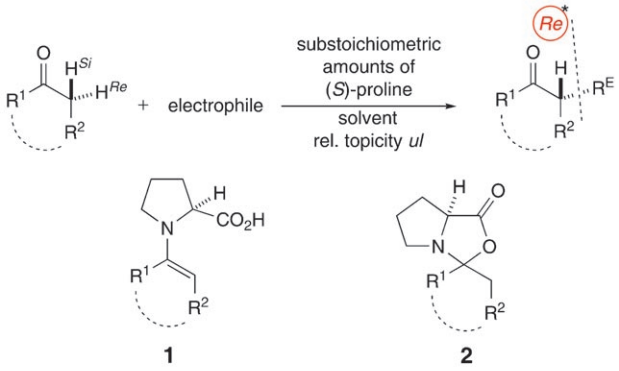
6) We use the *Cahn–Ingold–Prelog* nomenclature for specifying enantiotopic and diastereotopic trigonal faces and groups (*Re*, *Si*). In this nomenclature, *re*, *si* are used for reflection-invariant topicities [4].

7) For an elaborate density functional theory (DFT) calculation involving the oxazolidinone derived from alanine and cyclohexanone, see [6a]; the oxazolidinone is predicted by this method to be by *ca.* 4.5 kcal more stable than the corresponding enamine, for other theoretical studies on proline-catalysis by *Houk* and co-workers see [6b].

8) Self-condensations of aldehydes of type $R-CH_2CHO$ occur, and the oxazolidinone seen at first by IR disappears: *W. Prikoszovich*, hitherto unpublished results.

9) See p. 403 of [1].

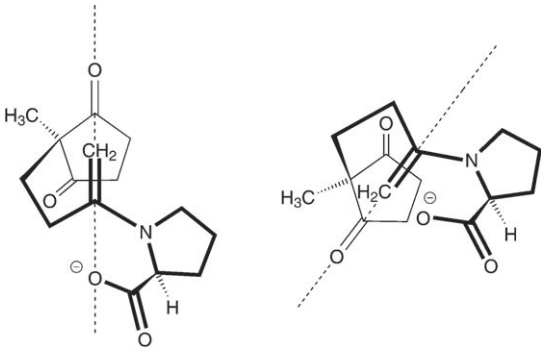
*Scheme 1*




* The designator of this enantiotopic face is *Si* when $R^2$ = OH (due to the *CIP* priority rules and not to a change of the stereochemical course of the reaction)

*Dunitz* and *Eschenmoser* groups: one of these reported X-ray crystal structures of a variety of enamines and discussed the possible role of N-pyramidality for the stereoselection in reactions of enamines with nucleophiles [9], and the other dealt with the X-ray crystal structure of a tricyclic N,O-ketene-acetal [10], a model compound prepared at the time in the same context. The recent initiative of the *Seebach* group took recourse to some of the unpublished results of that earlier work; therefore, it was thought that some of it would be required to be included in the present paper, providing at the same time the opportunity for eventually publishing some aspects of that earlier work.

***Short Summary of the Work Performed in the 1970's.*** That early work had been an attempt to respond to the challenge of a mechanistic rationalization of the (at the time) dramatic stereoselection observed in the proline-catalyzed aldolization step of the formation of the *Wieland–Miescher* ketone by *Hajos* and *Parrish* [11], and by *Eder*, *Sauer*, and *Wiechert* [12] in 1971/1974. The experimental effort was based on the conception of two hypothetical stereoselection factors, both stereoelectronic in nature: one of them referred to a possible role of the carboxylate group of the proline-substrate enamine derivative (see formulae **I** and **II**) in the sense that an intramolecular nucleophilic participation of a carboxylate O-atom in the product-determining step (presumed to be the electrophilic addition of a carbonyl C-atom to the enamine C=C bond) would prefer the *trans*-antiperiplanar mode (*i.e.*, **I**) as against the *trans*-lateral mode (*i.e.*, **II**). The other hypothesis considered the possibility of stereocontrol by a pyramidal geometry of the enamine N-center with a (local) sense of chirality that would be biased by the neighboring chirality center of the proline nucleus and, therefore, could cause stereoselection through a nucleophilic *trans*-participation of the N-atom lone-pair in the electrophilic addition of the C=O to the enamine C=C bond (see formulae **III** and **IV**). In experiments aiming at a synthesis of the enamine derived from proline and cyclohexanone for model studies, it was found that *N*-(trimethylsilyl)proline trimethylsilyl ester forms a stable oxazolidinone with pivalaldehyde (this paper, *Sect. 2*, *Scheme 3*), and that the oxazolidinone from cyclohexanone could be obtained by the same method and converted to the desired enamine-amidinium carboxylate (this paper, *Sect. 2*, *Scheme 4*) by treatment with a lipophilic amidine base, the synthesis of which (in another context) we had accomplished just about that time [13].



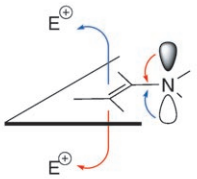
*trans*-antiperiplanar

**I**

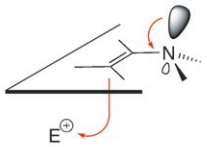


*trans*-lateral

**II**



**III**



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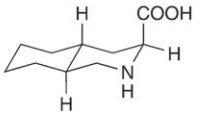
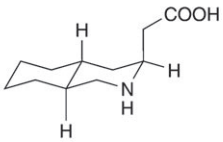
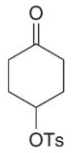


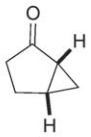
**V**



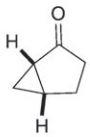
**VI**



**VII**



**VIII**



*ent*-**VIII**

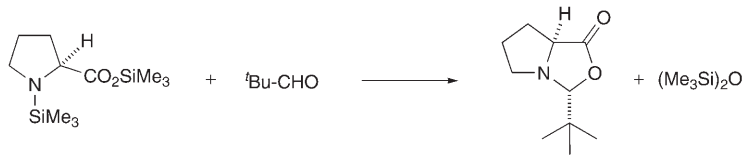
We designed a model reaction [2a] to find out whether enamines derived from L-proline (or from conformationally well-defined L-proline analogs such as **V** and **VI**) may display an intrinsic preference in the stereochemical course of electrophilic alkylation processes at the nucleophilic enamine C=C bond. The model reaction consisted in the conversion of the achiral 4-(tosyloxy)cyclohexanone **VII** to the chiral bicyclo[3.1.0] hexane-2-one (**VIII**) [14] brought about by reacting the ketone with L-proline (or **V** and **VI**) in the presence of molecular sieves (to induce the formation of oxazolidinone(s) and a tertiary organic base (to convert it to the enamine(s)). The samples of the bicyclic ketone (formed by intramolecular enamine alkylation and isolated in pure form after hydrolytic workup in yields below 50%) showed an absolute configuration (mostly (*R*)) that depended on the nature of the base and had

optical purities[10]) that hardly ever exceeded 10% (in solvents such as MeCN, DMF, DMSO, sulfolane (=tetrahydrothiophene 1,1-dioxide), $CH_2Cl_2$, using hindered and unhindered organic bases, reaction times 10–20 h, at room temperature). Optical yields were equally low, when the oxazolidinone intermediates were formed in benzene using the trimethylsilyl derivative of proline and the bicyclic amidine as the base. The highest optical yields of the (*S*)-bicyclo-ketone **VIII** were obtained by this method and using the bicyclic proline analogs **V** and **VI** (optical yields in both cases between 18 and 19%, as opposed to around 0% with proline and *ca.* 1% with homoproline under similar conditions). For experimental details, see *R. Hobi* [2a], p. 23–35 and 56–77, and for the synthesis of the proline analogs **V** and **VI**, see [2b][2c][9].

The model reaction clearly did *not* reveal an intrinsic preference in the stereochemical course of an electrophilic alkylation of a proline-derived enamine as it was hoped it would do. Instead, its results pointed to an exceptional sensitivity to conditions of the stereochemical outcome of such a reaction. This implied that no conclusion could be drawn from the model study with regard to the mechanism of the stereoselection observed by *Hajos* and *Parrish* [11], and by *Eder et al.* [12].

**2. Preparation of Proline-Derived Oxazolidinones.** – We had actually first isolated[3]) the proline-derived oxazolidinone **2a** in 1975. It was prepared from *Rühlmann*'s doubly silylated proline [15] and pivalaldehyde (*Scheme 2*). By this procedure, or mild acid-catalyzed condensation conditions [16], we have also prepared analogous bicyclic compounds from the cysteine-formaldehyde acetal ('thiaproline' → **2b**) [16b][17], from hydroxyproline (→ **2c**) [18], and from azetidine-2-carboxylic acid (→ **2d**) [16b][19]. The bicyclic oxazolidinones **2a**–**2d** and the monocyclic *N*-acyl-oxazolidinones **3a** (from non-cyclic amino acids) [20] were used for the preparation – through Li-enolates – of $\alpha$-branched amino acids with *self-regeneration of the stereogenic centers* (SRS) [21] (**2a**–**d** → **2e** → **4** and **3a** → **3b** → **5**)[11]).

*Scheme 2*




**2a**

While the *N*-acyl derivatives of type **3** are quite stable[12]), the bicyclic oxazolidinones **2** are difficult to purify and isolate on a preparative scale[13]) for two reasons: *i*) They must be handled under exclusion of moisture; neat liquid samples or solutions in common organic solvents turn cloudy on contact with air, due to formation of the insoluble amino acids. *ii*) They undergo decarboxylation at elevated temperatures, with

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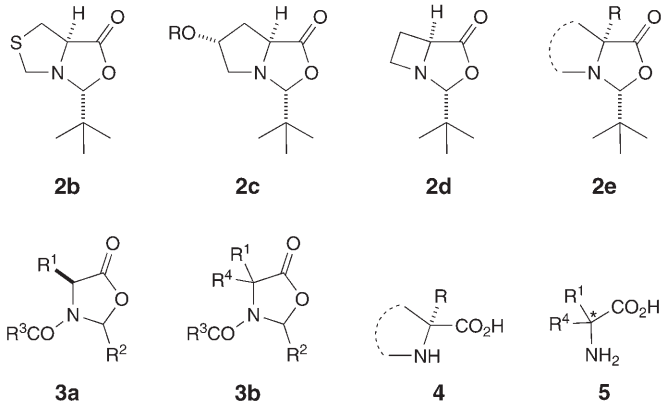
10) Determined from CD spectra of product samples (see [2a] and [14]). At the time these experiments were conducted, no chiral columns for GC or HPLC determination of enantiomer ratios were available. Therefore we use the outdated terms 'optical purity' and 'optical yield' here.

11) Dozens of enantiomerically pure 2-substituted proline derivatives of type **4** are now commercially available and are used as 'pharmacophores' (*cf. Sigma-Aldrich* catalog).

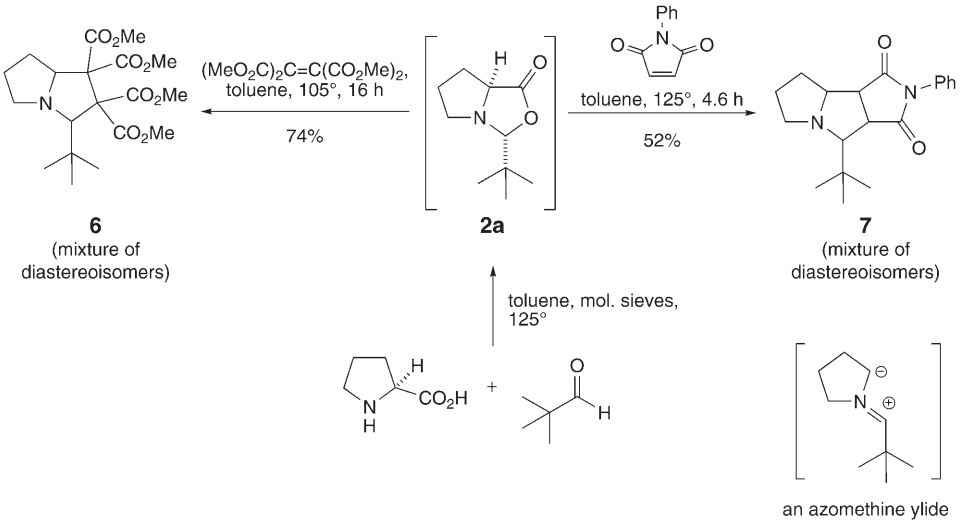
12) Compound **3a** ($R^1$ = H, $R^2$ = $^t$Bu, $R^3$ = Ph) racemizes upon heating in refluxing MeCN [20b], probably through a zwitterion $^t$Bu–CH=$N^+$(COPh)$CH_2CO_2^-$.

13) For a 45-g-scale preparation of the bicyclic oxazolidinone **2a**, see the *Organic Syntheses* Procedure [16c]. We do not consider the *in-situ* formation and NMR identification of a compound in solution a 'preparation' (*cf.* supplementary material in [8b]).




generation of azomethine ylides, which can be trapped by dipolarophiles[14]), as shown for oxazolidinone **2a** in the reaction with tetrakis(methoxycarbonyl)ethylene (→**6**) or *N*-phenylmaleinimide (→**7**; *Scheme 3*)[3])[4])[5])[14])[15])[16]).

Scheme 3. *Thermolytic Decarboxylation of the Oxazolidinone* **2a** *from Proline and Pivalaldehyde in the Presence of 1,3-Dipolarophiles.* An azomethine ylide is the most likely reactive intermediate (*cf. Scheme 4*). The experiments were performed in the 70's; for **6**, we were not able to retrieve a procedure. As described in the *Exper. Part*, **2a** was generated *in situ* (proline, pivalaldehyde, molecular sieves) for the reaction leading to **7**.




[14]) Decarboxylations in reactions of carbonyl compounds with amino acids have actually been discovered by *Strecker* [22], and *Curtius* and *Lederer* [23] almost 150 years ago: $R^1-CO-R^2+R^3-CH(NH_2)-CO_2H \rightarrow R^1-CH(NH_2)-R^2+R^3-CHO+CO_2$

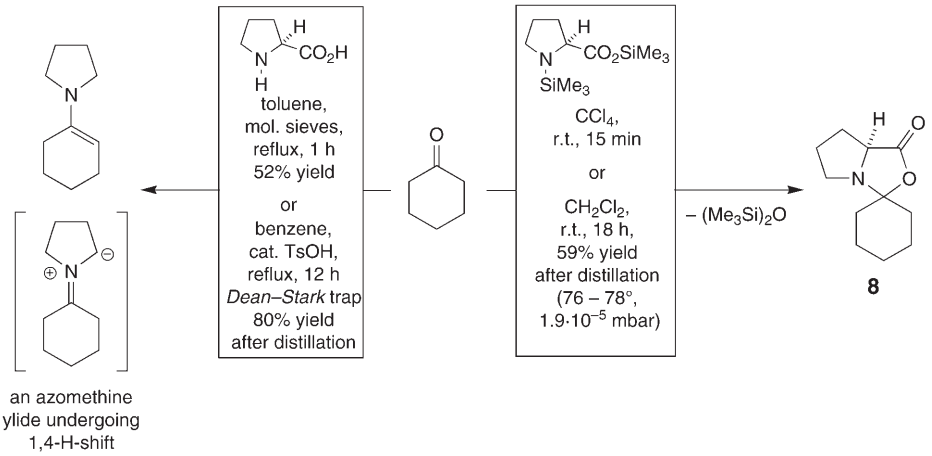
[15]) For some more recent investigations of these types of reactions, see [24].

[16]) Products of '1,3-dipolar cycloadditions' [25] of ylides of the type shown in *Schemes 3* and *4* have been described as 'side-products' of proline-catalyzed transformations, (*cf.* [26]).

Triggered by reports on proline-catalyzed *Michael* additions of ketones to nitro-olefins from the *Enders* [27a] and *List* [27b] laboratories, knowing that a nitro-olefin does not require any acid activation[17]) to react with an enamine [28][29], and remembering that we had, once upon a time[3]), isolated the cyclohexanone-derived oxazolidinone **8**, we decided to study its reactions with 'super-electrophiles', such as (*E*)-*β*-nitrostyrene and chloral (=trichloroacetaldehyde).

The preparation of larger amounts of the tricyclic spiro-oxazolidinone **8** is, again, a challenge (*Scheme 4*): at higher temperatures, the condensation of cyclohexanone with proline cleanly leads to 1-(cyclohex-1-enyl)pyrrolidine (pyrrolidino-enamine of cyclohexanone; NMR spectrum in *Fig. 1,a*). Decarboxylation also occurs when the desired product **8**, prepared from the ketone and silylated proline at room temperature, is distilled under insufficient vacuum[18]). Contact of the distilled colorless liquid **8** with air or dissolution in aprotic solvents that are not rigorously dry causes precipitation of proline[19]). However, kept in a freezer and tightly protected from contact with moisture, oxazolidinone **8** is a 'well-behaved' compound, which can be handled with anaerobic syringe techniques; its NMR spectra and part of its IR spectrum are shown in *Fig. 1,b* and *c*, and *Fig. 2* (red curve), respectively.

Scheme 4. *Preparation of the Spiro-oxazolidinone* **8** *from Cyclohexanone and Proline, and Thermal Decarboxylation of* **8** *to 1-(Cyclohex-1-enyl)pyrrolidine*[3]). Distillation of **8** is only possible under turbo-pump vacuum.




**3. Reactions of the Oxazolidinone 8 with Electrophiles.** – With a good supply of the oxazolidinone **8** at hand, we were able to study its reaction with *β*-nitrostyrene. As solvent we used THF, an uncommon medium for catalysis by proline, which is insoluble

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17) Invoked in all generally accepted mechanistic proposals of proline catalysis [3][5][6b][27] (see section on mechanism, below).

18) The use of a special '*Aldrich* Kugelrohr oven' is described in an *Organic Syntheses* procedure for the preparation of **2a** [16c].

19) The deliberate hydrolysis is used for analytical purposes to show that no racemization of proline has occurred. The specific rotation of (*S*)-proline is $[\alpha]_D^{20} = -85$ ($c = 4$, $H_2O$) [30b].

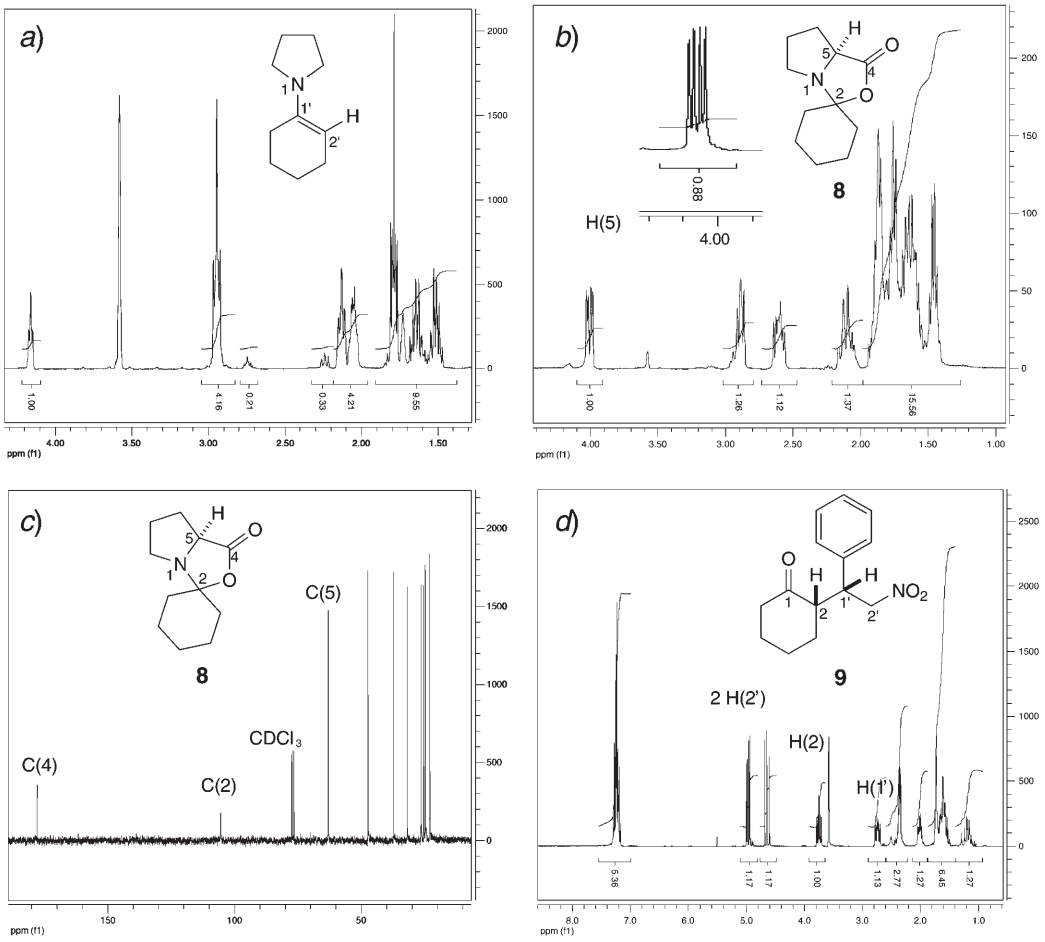


Fig. 1. *NMR Spectra of oxazolidinone* **8** ($^1$H-NMR in ($D_8$)THF, $^{13}$C-NMR in $CDCl_3$; *b* and *c*), *of 1-(cyclohex-1-enyl)pyrrolidine in (*$D_8$*)THF* (*a*), *and of nitro ketone* **9** *in (*$D_8$*)THF d*). Compound **9** was isolated after reaction of **8** with $\beta$-nitrostyrene in THF and aqueous workup. Only the characteristic low-field signals are assigned in these presentations (*cf.* [29a][30a], the data of the 2D-NMR spectrum of *Fig. 3*, and the *Exper. Part*). The $^1$H-NMR spectra shown here were recorded in ($D_8$)THF, because the reaction of **8** with $\beta$-nitrostyrene was performed and NMR-spectroscopically followed in this solvent (*Fig. 3*). The small signal in *b*) at 4.15 ppm arises from a trace of the pyrrolidino-enamine (*cf. a*)) in the oxazolidinone **8** sample used.

in THF. In fact, an extremely slow conversion between cyclohexanone and $\beta$-nitrostyrene takes place in this solvent with suspended proline (18% of adduct **9** after 7 d at room temperature, ds 97%, er 75:25)[20]. On the other hand, when a THF solution of an equimolar mixture of oxazolidinone **8** and $\beta$-nitrostyrene is kept at room

[20]) For a 22-h reaction time, a 7% yield, a ds of 98%, and an er of 78:22 were reported by *Barbas* and co-workers [31].

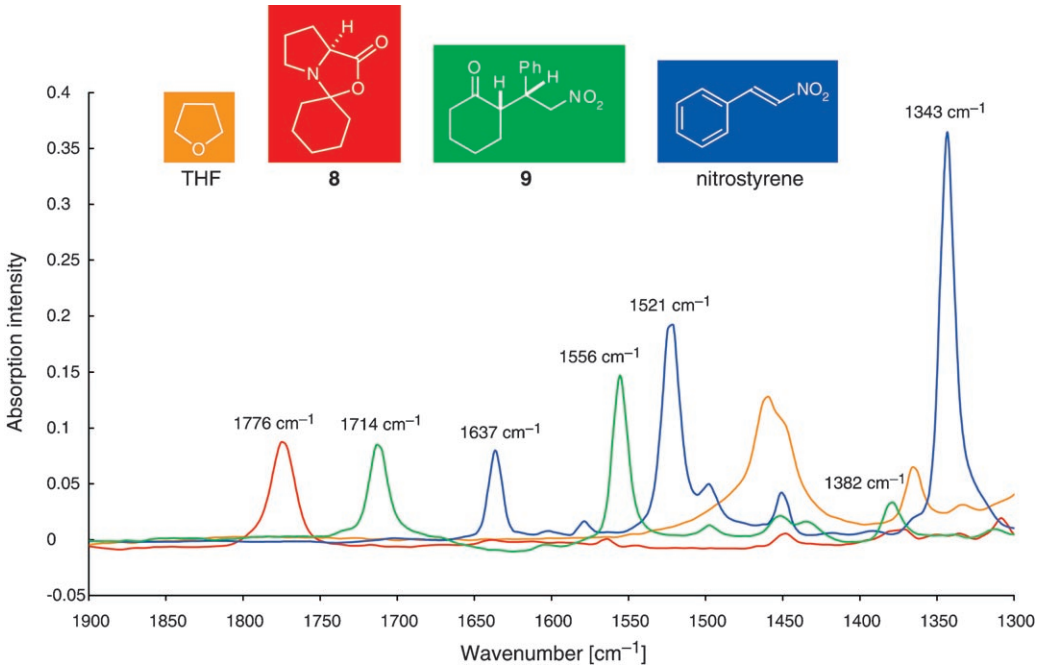


Fig. 2. *Section from the 1900–1300-cm$^{-1}$ region of the IR spectra of THF* (*orange*), *of the oxazolidinone* **8** (*red*), *of β-nitrostyrene* (*blue*), *and of the nitro ketone* **9** (*green*). The spectra were recorded as THF solutions, and the THF bands near 1460 and 1360 cm$^{-1}$ were electronically removed. The same wavenumber section was used to follow the reaction of **8** with *β*-nitrostyrene in THF (see *Fig. 4*).

temperature for 4.5 h, an 85% conversion to a compound **x** is observed by NMR analysis (of a run in ($D_8$)THF; see *Sect. 4*). Hydrolysis and workup lead to isolation of the nitro ketone **9** of high diastereoisomer purity and poor enantiomer purity (*Scheme 5*), a stereochemical outcome which is also typical for the proline-catalyzed reaction in DMSO or in MeOH [27].

Since enamines of type **1** must be the nucleophiles in proline-catalyzed reactions of carbonyl compounds with electrophiles [3c][6b], and since an enamino-carboxylate **11** or -carboxylic acid **12** is nothing but a product of HX elimination in the oxazolidinone **8** (*Scheme 6*), we next added catalytic amounts of DBU (=1,8-diazabicyclo[5.4.0]undec-7-ene)[21][22] to a *ca.* 1:1 mixture of **8** and *β*-nitrostyrene in THF at dry-ice temperature. We were pleased to see that the reaction took place, as evidenced by quenching and isolation of the nitro ketone **9** at this low temperature. Thus, the reaction of *β*-nitrostyrene with the oxazolidinone **8** is base-catalyzed! In the room-temperature

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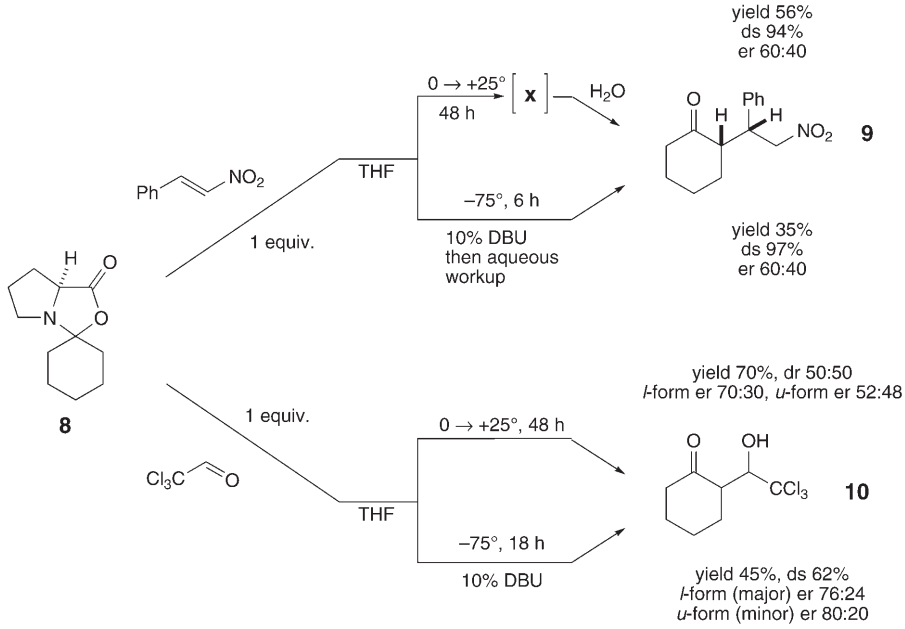
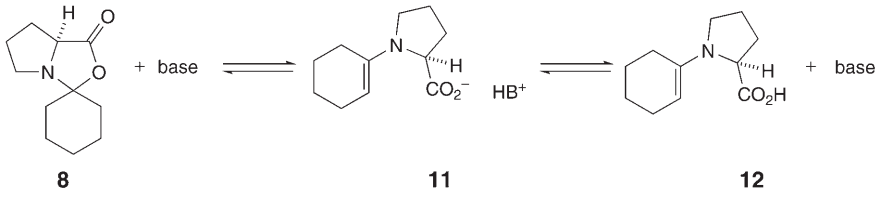
[21] p$K_a$ of $HB^+$ in MeCN (in $H_2O$) DBU: 24.34 [33a], 1,2,2,6,6-pentamethylpiperidine: 18.6 (11.3) [33b], *Hünig*'s base (DIPEA ($EtN^iPr_2$)): (11.44) [33c], *Heinzer*'s base: (>12) [13], $Et_3N$: 18.82 (10.71) [33a][33d], *Schmidtchen*'s base: 29.96 [33e].

[22] When DBU and *β*-nitrostyrene are allowed to react in the absence of **8**, an insoluble precipitate is formed in THF; probably DBU causes the *β*-nitrostyrene to polymerize (*cf.* the use of DBU in the *Baylis–Hillman* reaction of *α,β*-unsaturated carbonyl compounds [34]).

Scheme 5. *Non-Catalyzed Reactions of the Spiro-oxazolidininone* **8** *with β-Nitrostyrene and Chloral at Room Temperature and DBU-Catalyzed Reactions at Dry-Ice Temperature.* DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene. ds = diastereoselectivity; er = enantiomer ratio; we do strongly favor the abandonment of the old-fashioned term ee [32].




*Scheme 6*




reaction, the base is possibly **8** itself – it contains a sterically encumbered tertiary amino N-atom[21]). Indeed, when *Hünig*'s base (DIPEA)[21]) was added to the reactants at a temperature, at which the uncatalyzed reaction is very slow (– 75° in THF), product formation was also observed, albeit much more slowly than with DBU.

Besides *β*-nitrostyrene, we also employed chloral as a 'super-electrophile' in the reaction with oxazolidinone **8**. Chloral and other highly reactive aldehydes, which form stable hydrates, are considered poor candidates as electrophiles for proline-catalyzed transformations [35][36a]. As outlined in *Scheme 5*, chloral reacts with the oxazolidinone **8** in THF at room temperature in an uncatalyzed transformation and at – 75° under DBU catalysis to provide, after aqueous workup, the aldol **10**.

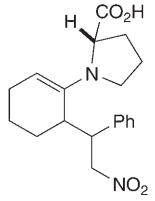
The results obtained in the reaction of the oxazolidinone **8** with *β*-nitrostyrene and with chloral are collected in *Table 1*.

Table 1. *Yields and Stereoselectivities of Reactions of Oxazolidinone* **8** *with β-Nitrostyrene* (→ **9**) *and with Chloral* (→ **10**) *in THF* (0.25M), *Carried out under Various Conditions* (*cf. Scheme 5*)

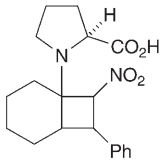
| Product | Temp. [°] | Time [h] | DBU [equiv.] | DIPEA [equiv.] | Yield [%] | ds [%] | er |
|---|---|---|---|---|---|---|---|
| **9** | 0 → 25 | 48 | – | – | 56 | 94 | 60 : 40 |
| | – 45 | 48 | – | – | 49 | 96 | 60 : 40 |
| | – 75 | 1 | – | – | < 2 | n.d. | n.d. |
| | – 75 | 18 | – | – | 2[a]) | n.d. | n.d. |
| | – 75 | 6 | 0.1 | – | 35 | 97 | 60 : 40 |
| | – 75 | 18 | 1.0 | – | 9[b]) | 95 | 55 : 45 |
| | – 75 → – 70 | 68 | – | – | 5[c]) | n.d. | n.d. |
| | – 75 | 1 | – | 0.1 | 4[c]) | n.d. | n.d. |
| | – 70 | 68 | – | 0.1 | 43[c]) | n.d. | n.d. |
| **9**[d]) | 25 | 168 | – | – | 18 | 97 | 75 : 25 |
| **10**[e]) | 0 → 25 | 48 | – | – | 70 | 50 | *l*-**10** 70 : 30 |
| | | | | | | | *u*-**10** 52 : 48 |
| | – 75 | 18 | 0.1 | – | 45 | 62[f]) | *l*-**10** 76 : 24 |
| | | | | | | | *u*-**10** 80 : 20 |

[a]) Yield determined by $^1$H-NMR with an internal standard. [b]) Nitro-styrene was added 15 min after the DBU salt (see **19** in *Scheme 8*) had been formed. [c]) Conversion relative to remaining *β*-nitrostyrene. [d]) Cyclohexanone/proline/*β*-nitrostyrene 1 : 1 : 1, THF (0.25M). [e]) *u*-**10** Formed in excess has (2*R*,1′*S*)-configuration [36], the absolute configuration of *l*-**10** is unknown. [f]) *l*-**10** Is formed in excess in this case.

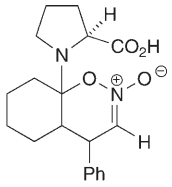
*Determination of the Structure of* **x** (*Scheme 5*). The reaction of oxazolidinone **8** with *β*-nitrostyrene was followed by NMR measurements and with an IR probe (both in ($D_8$)THF). If we take it for granted [3][5][6b] that the nucleophilic species in the C,C-bond-forming step is an enamine derivative (*i.e.*, **11**, **12**), we have to consider the four species **13**–**16** as primary products of reactions with the nitro-olefin. 'Normal' achiral [28] and chiral [29][37] pyrrolidino- and piperidino-enamines of cyclohexanone



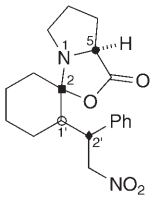

**13**




**14**




**15**




**16**

| | a | b | c | d | e | f | g | h | |
|---|---|---|---|---|---|---|---|---|---|
| ● | *S* | *S* | *S* | *S* | *S* | *S* | *S* | *S* | ← (proline center) |
| ■ | *S* | *S* | *S* | *R* | *R* | *R* | *R* | *S* | |
| ○ | *S* | *S* | *R* | *S* | *R* | *R* | *S* | *R* | |
| ♦ | *S* | *R* | *S* | *S* | *R* | *S* | *R* | *R* | |

relative configuration *unlike* (*u*) at position 1′/2′
of the major nitroketone diastereoisomer **9**

and nitro-olefins react spontaneously in ethereal solvents at temperatures between $-75°$ and $+20°$. Thus, a solution in $Et_2O$ of a $\beta$-nitrostyrene immediately turns brownish upon addition at $-75°$ of the enamine prepared from prolinol ether and cyclohexanone [29a]; no catalysis is required. The product of aqueous workup is a nitro ketone of type **9**, while non-aqueous workup leads to isolation of the enamine derived from that nitro ketone (*cf.* **13**). Besides such nitro ketone enamines, cyclobutanes, and cyclic nitronic acid esters [28][23])[24]), products of formal [2+2] and [4+2] cycloadditions have been identified as primary products formed from nitro-olefins and enamines. All these primarily formed compounds give the nitro ketones upon hydrolysis. Thus, the intermediates **13**, **14**, or **15** could be the species **x** present before aqueous workup of the reaction of the oxazolidinone **8** with $\beta$-nitrostyrene.

Our IR and NMR analyses rule out all three of these possible primary adducts: *i*) the NMR spectrum contains the typical *dd* signals of $O_2N-CH_2$ groups (not in **14** and **15**); *ii*) there is no typical signal from the vinylic H-atom of a cyclohexanone enamine (as in **13**), which appears as a broad *triplet* near 4.1 ppm (*cf. Fig. 1,a*); *iii*) there is only a barely detectable $^1$H-NMR *multiplet*, which could be assigned to C*H*=N(O)OR (*ca.* 6.5 ppm [38]), and which would have to arise from **15**. Oxazolidinones derived from proline show two distinct spectroscopic features: *i*) The H-atom at the bridgehead between the two five-membered rings (H–C(5)) gives rise to a typical sharp *dd* NMR signal between 3.8 and 4.4 ppm, depending upon the substituent(s) at C(2) and the solvent used for the measurement [5][7][8][16–19]; as the reaction of oxazolidinone **8** (H–C(5) at 4.0 ppm; see *Fig. 1,a*) with $\beta$-nitrostyrene proceeds, new *dd* signals appear nearby, together with the afore mentioned $O_2N-CH_2$ signals (*Fig. 3*). *ii*) In the IR spectrum of the bi- and tricyclic oxazolidinones **2a**–**2e** and **8**, there is a characteristic C=O bond near 1770 $cm^{-1}$; this band never disappears in the course of the reaction of **8** with $\beta$-nitrostyrene (*Fig. 4*). A 2D-NMR spectrum in ($D_8$)THF of the reaction mixture formed from the oxazolidinone **8** and $\beta$-nitrostyrene is presented in *Fig. 3*. Clearly, there are several diastereoisomers of the compound which must be **16**, the *product oxazolidinone*. Of the eight stereoisomers **16a**–**16h** we may consider only four (**16b**, **16c**, **16f**, and **16g**), *i.e.*, the ones which have the observed relative configuration *u* of the product of hydrolysis, the nitro ketone **9**, since it is formed with $\geq 95\%$ diastereoselectivity. In the NMR spectrum of the reaction mixture, we see signals of two major and two minor diastereoisomers, but there is no way to achieve an assignment at this point of the investigation[25])[26])[27]).

We have thus established that an oxazolidinone, such as the one derived from proline and cyclohexanone, undergoes rapid reactions at room temperature in the non-

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[23]) *Cf.* the hetero-*Diels–Alder* adducts of nitro-olefins and enol-ethers [38].

[24]) For DFT calculations of such [4+2] cycloadducts (*cf.* **15**) from $\beta$-nitrostyrene and the cyclohexanone-enamine of a bicyclic 2-(aminomethyl)pyrrolidine triflamide derivative, see [39].

[25]) One way of assignment would be to prepare compound **16** from an enantiomerically pure sample of **9** and bis(trimethylsilyl)-(*S*)-proline, so that only two of the diastereoisomeric products **16** can be formed, which are epimeric at the spiro center (*cf.* [8a]).

[26]) We will study reactions of other oxazolidinones with a variety of electrophiles, from which less complex products are formed in higher overall enantioselectivities (*cf.* **10**).

[27]) Also the oxazolidinone from proline and acetone will be a candidate for studying products of reactions with electrophiles that can be more easily analyzed.

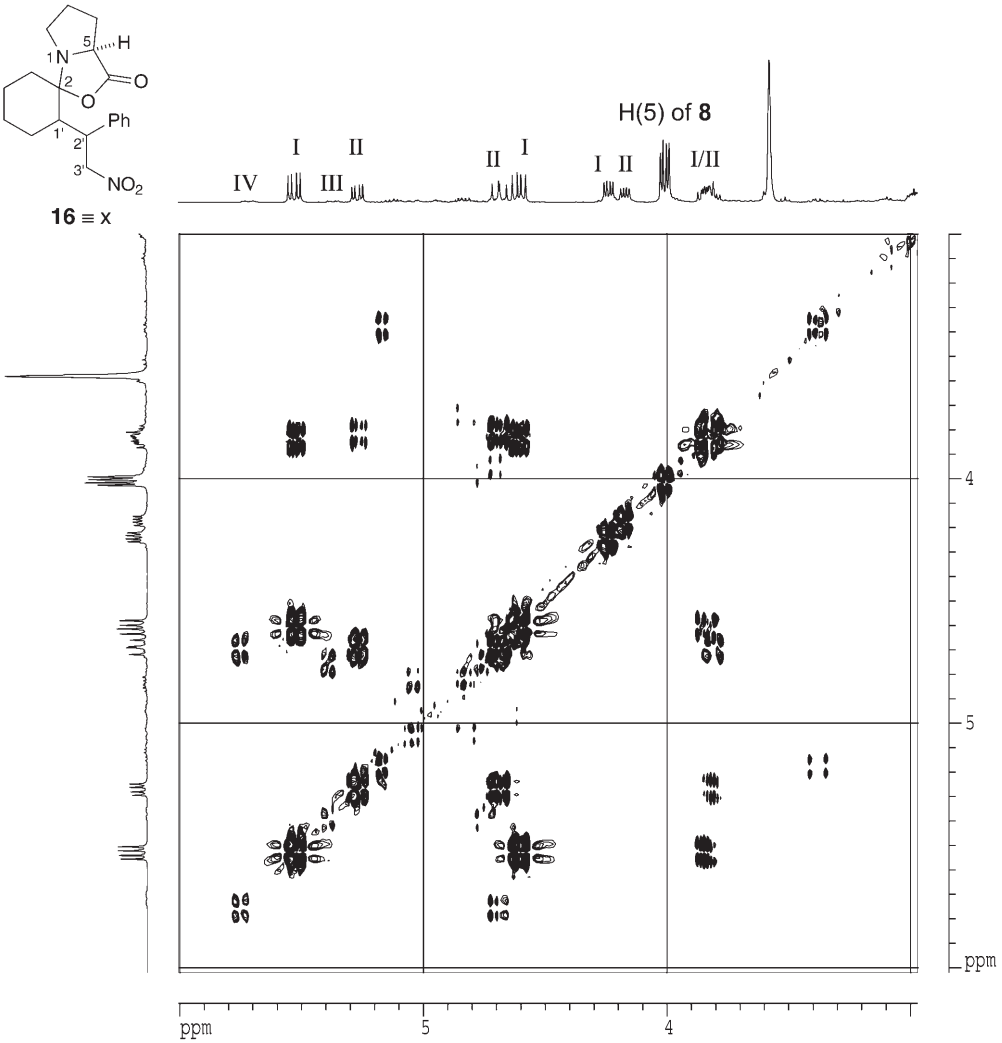



Fig. 3. *Section from 3–6-ppm region of the 400-MHz 2D-$^1$H-NMR spectrum of a reaction mixture of oxazolidinone* **8** *and β-nitrostyrene in ($D_8$)THF in an NMR tube.* The four lowest-field *dd* signals I, II, III, IV arise from one of the α-$NO_2$–$CH_2$ H-atoms H(3′). Clearly, there are two major (I and II) and two very minor diastereoisomers (III and IV). The *dd* sets from the second α-$NO_2$–$CH_2$ H-atoms H(3′) of the two major diastereoisomers appear at higher field (4.7 and 4.6 ppm). The benzylic H-atoms H(2′) of the diastereoisomers are observed around 3.8 ppm. The characteristic *dd* signal of the bridgehead H-atom in the starting material **8** is detected at 4.0 ppm, and there are two additional *dd* signals at 4.25 and 4.18 ppm arising from H(5) of the product oxazolidinones, in a ratio matching that of the two sets from the α-$NO_2CH_2$ H-atoms. From comparison of the intensities of these bridgehead-H-atom signals, it is suggested that the ratio of product **16** (≡ **x**) and starting material **8** is close to 1:1 at the point in time of the measurement.

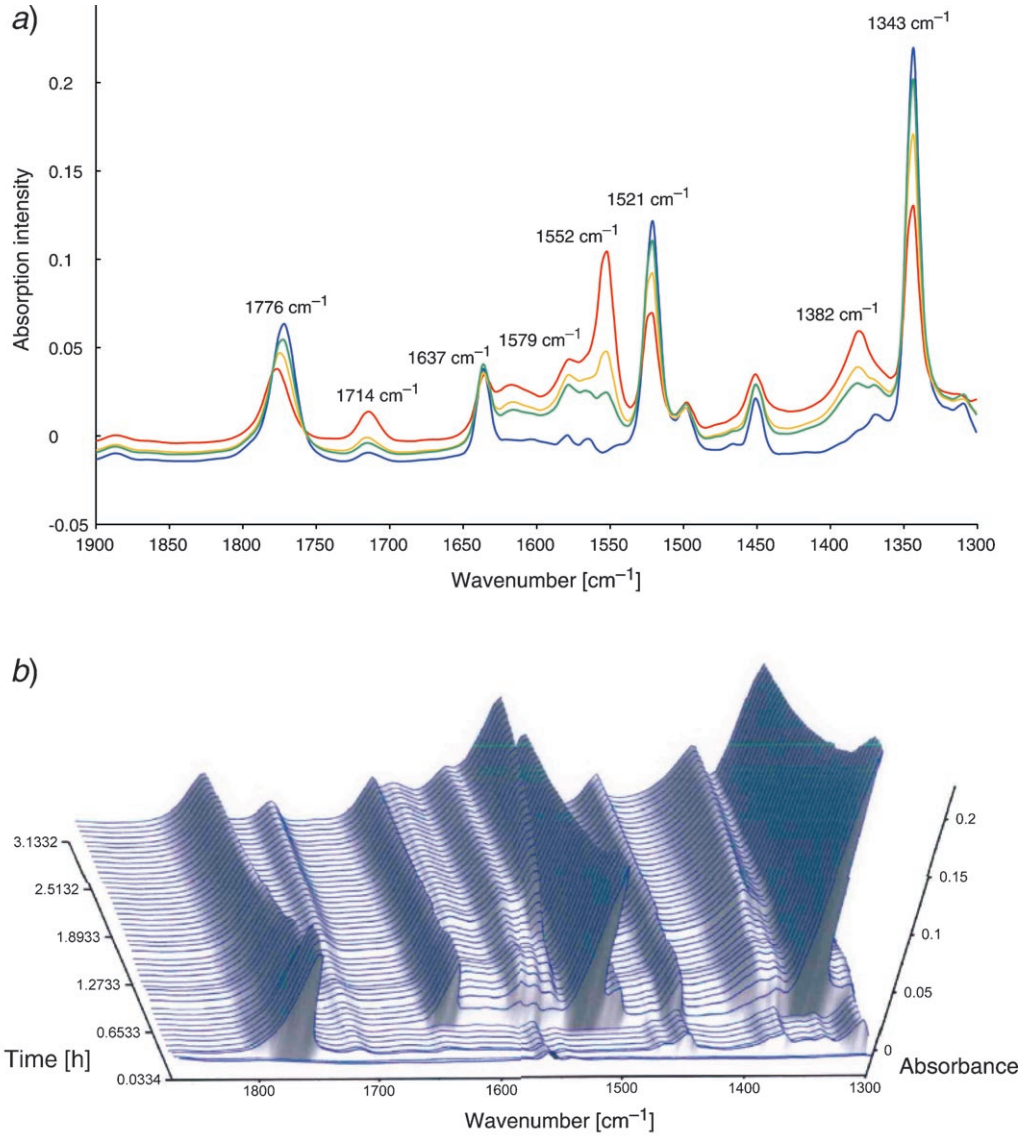
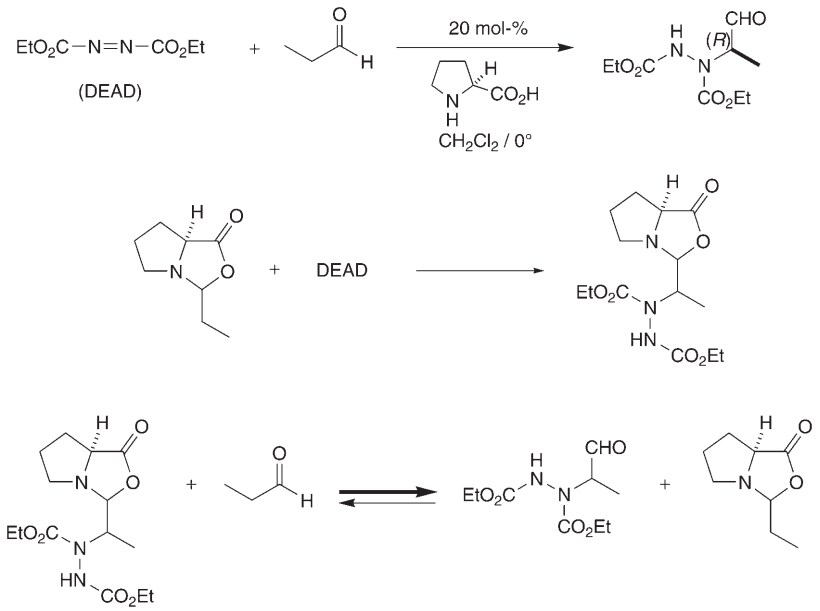



Fig. 4. *Course of the reaction of oxazolidinone* **8** *with β-nitrostyrene* (in ($D_8$)THF from 0° to room temperature) *followed by IR spectroscopy* ('ReactIR'). Clearly, the characteristic oxazolidinone IR absorption near 1775 $cm^{-1}$ does not disappear as the reaction proceeds. The band at 1714 $cm^{-1}$ arising from nitro ketone **9** is an indication that moisture was not rigorously excluded from this experiment. For assignment of the various bands to the components of the reaction mixture, see also *Fig. 2*. *a*) Reaction times and temp.: 0 min, 0° (*blue*); 18 min, 10° (*green*); 48 min, 15° (*orange*); 150 min, room temperature (*red*); *b*) 3D presentation of the course of the reaction.

polar solvent THF with *β*-nitrostyrene or chloral as electrophiles, and that the reaction occurs even at dry-ice temperature when catalyzed with a base. Remarkably, the primary product of reaction with *β*-nitrostyrene is again an oxazolidinone.

**4. Oxazolidinones in the Proline-Catalyzed Reaction of Propanal with Diethyl Azodicarboxylate – *Blackmond*'s Observations.** – In an effort to elucidate the 'auto-inductive' reaction [8] of the proline-mediated additions of propanal to nitrosobenzene [40] and to diethyl-azodicarboxylate (DEAD) [41] (*Scheme 7*), *Blackmond* and co-workers have made the following observations based on *in-situ* NMR measurements in $CD_2Cl_2$ [8a][8b]: *i*) in a solution containing the oxazolidinone from proline and propanal, and the electrophile DEAD, the product oxazolidinone is the main detectable resulting species (*Scheme 7*). *ii*) The product oxazolidinone and propanal react to give the actual product and the oxazolidinone derived from propanal (*Scheme 7*). Thus, like in our case (**8** + $\beta$-nitrostyrene → **x** (≡**16**)), the spectroscopic analysis of the reaction reveals that an oxazolidinone is the reactant and the product in the stoichiometric transformation with an electrophile under anhydrous conditions. The 'autocatalysis' could actually arise through a base catalysis, since a compound such as the hydroxylamine derivative (generated in the reaction with nitrosobenzene) is expected to be a reasonably strong base; *cf.* the pronounced base catalysis in our reactions of oxazolidinone **8** with $\beta$-nitrostyrene and chloral in THF at $-75°$ (*Scheme 5*). This interpretation requires enamine formation from an oxazolidinone to be the rate-limiting step.

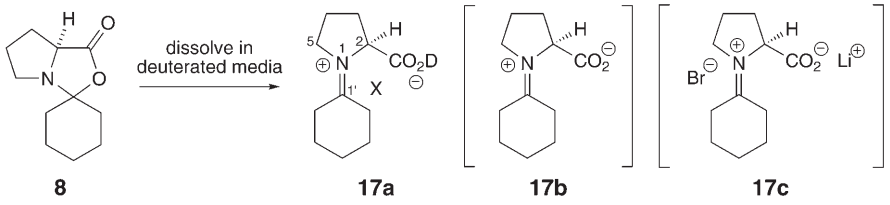
*Scheme 7*




**5. Reactions of Oxazolidinone 8 with Acids, Bases and LiBr.** – We have seen that oxazolidinones **2** and **8** are labile to heat and moisture, and we wondered about their stability against non-aqueous acids and bases.

Thus, we first dissolved the cyclohexanone derivative **8** in anhydrous protic solvents and acids of decreasing p$K_a$, and recorded NMR and IR spectra of the resulting solutions (*ca.* 1M in **8**, +20°). We chose $CD_3OD$, ($D_6$)phenol, ($D_2$)hexafluoroisopropanol (($D_2$)HFIP=$(CF_3)_2CDOD$), $CD_3COOD$, and $CF_3COOD$ ((D)TFA) as solvents. Strikingly, the characteristic carbonyl band of **8** is absent in the rather weak acid HFIP, and a new peak appears in the IR spectrum at 1660 $cm^{-1}$ (assigned to $C{=}NR_2^+$). Likewise, the typical signal from the bridgehead H-atom of **8** (*ca.* 4 ppm) is absent in ($D_2$)HFIP, and a new signal at 4.7 ppm is observed. Finally, the $^{13}$C-signal of the spiro-C-atom of **8** (*ca.* 100 ppm; *cf. Fig. 1,c*) is absent in all five solvents, and a low-field $^{13}$C-signal of a C-atom not bearing any H-atom is observed between $\delta$ 190 and 200 ppm (assigned to $^{13}C{=}NR_2^+$). Obviously, a compound other than the oxazolidinone is present in these media (see the characteristic NMR data in *Table 2*). We assign the iminium acid **17a** or the zwitterionic structure **17b** to the compound arising from **8** in the protic solvents[28]). To see how many equivalents of the protic substances are required for the opening of the oxazolidinone ring, we added increasing amounts of MeOH, PhOH, and HFIP to $C_6D_6$ solutions of **8** at room temperature in an NMR tube. From the data shown in *Table 3*, it is evident that shifts characteristic of the species **17** observed in neat $CD_3OD$, $C_6D_5OD$, and ($D_2$)HFIP are observed with 6 equiv. of

Table 2. *Dissolution of Oxazolidinone* **8** *in Solvents of Increasing Acidity Generates Iminium Acid Derivatives* **17**, *as Deduced from $^1$H- and $^{13}$C-NMR Data*. In a LiBr-saturated ($D_8$)THF solution, the oxazolidinone is also ring-opened. For description of the complete spectra, see *Exper. Part*.



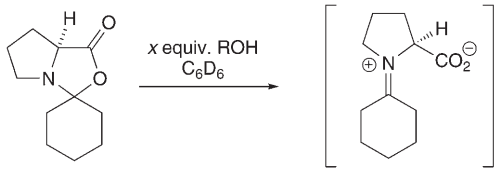

**8** **17a** **17b** **17c**

| Medium | p$K_a$ [$H_2O$] | $\delta$($H$–C(2)) | $\delta$($CH_2$(5)) | $\delta$(C(1′)) | $\delta$($CO_2$H) |
|---|---|---|---|---|---|
| $D_3COD$ | 15.5 | 4.83 (*dd*) | 4.14 (*ddd*), 3.98 (*ddd*) | 190.7 | 172.5 |
| $C_6D_5OD$[a]) | 10.0 | 4.49 (br. *d*) | 2.88 (*dt*), 3.37–3.42 (*m*) | 191.9 | 173.1 |
| ($D_2$)HFIP[b]) | 9.3 | 4.73 (br. *t*) | 3.78 (*dt*), 4.16 (*dt*) | 195.9 | 175.7 |
| $D_3CCO_2D$ | 4.5 | 4.87 (*dd*) | 3.72–3.82 (*m*), 3.86–3.94 (*m*) | 192.2 | 172.6 |
| $F_3CCO_2D$ | –0.2 | 4.86 (br. *d*) | 3.60–3.70 (*m*), 3.77–3.81 (*m*) | 200.1 | 175.1 |
| LiBr/($D_8$)THF | – | 5.33 (br. *d*) | 4.08–4.27 (*m*) | 190.8 | 173.7 |
| ($D_6$)DMSO | – | 4.21 (*ddd*) | 2.91–2.96 (*m*), 2.64 (*td*) | 107.1 (trace) | 176.9 |

[a]) NMR Measurements were performed at 50° to ensure that the solvent would be a fluid liquid.
[b]) HFIP = $(CF_3)_2CHOH$.

[28]) In the weakly acidic solvents MeOH and HFIP, the zwitterion is more likely to be present, in TFA the iminium-acid should prevail.

Table 3. *'Titration' of the Oxazolidinone* **8** *with MeOH, PhOH, and $(CF_3)_2CHOH$ (HFIP) in $C_6D_6$ Solution with $^1H$- and $^{13}C$-NMR Analysis.* With MeOH, the $^{13}C$-signal of the iminium C-atom (*ca.* 190 ppm) is not seen under these conditions, but the *ca.* 0.8-ppm downfield shifts of the $HCCO_2$ and $H_2CN$ H-atom signals is in the same range as in neat MeOH (*cf. Table 2*). Three equiv. of PhOH and HFIP are sufficient to cause ring-opening. Note that the chemical shifts in *Tables 2* and *3* cannot be identical, because all values in *Table 3* were obtained in ($D_6$)benzene, while those in *Table 2* were recorded in a wide range of other solvents.




**8** **17b**

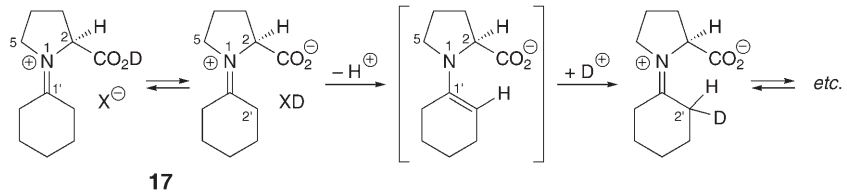
ROH = MeOH, PhOH, HFIP

| Equiv. MeOH | $\delta(CHCO_2)$ | $\delta(CH_2N)$ | $\delta$(C=N or O–C–N) | $\delta(CO_2)$ |
|---|---|---|---|---|
| 0 | 3.68 (*dd*, *J* = 9.5, 4.8) | 2.42–2.47 (*m*), 2.16 (*q*, *J* = 8.8) | 100.7 | 177.5 |
| 0.05 | 3.70 (*dd*, *J* = 9.2, 5.1) | 2.44–2.49 (*m*), 2.18 (*q*, *J* = 8.8) | 100.9 | 177.5 |
| 0.5 | 3.73 (*dd*, *J* = 9.0, 5.2) | 2.49 (*ddd*, *J* = 8,9, 4.4, 3.1), 2.22 (*q*, *J* = 8.9) | 104.4 (trace) | 177.4 |
| 1 | 3.82 (*dd*, *J* = 9.2, 4.7) | 2.56 (*ddd*, *J* = 5.5, 5.1, 3.2), 2.36 (*td*, *J* = 9.5, 6.9) | – | 176.9 |
| 3 | 4.19 (br. *d*, *J* = 7.5) | 2.95 (br. *t*, *J* = 5.8) | – | 174.0 |
| 6 | 4.44 (*dd*, *J* = 8.5, 1.9) | 3.33–3.46 (*m*), 3.15–3.25 (*m*) | – | 171.9 |
| 12 | 4.43 (br. *d*, *J* = 8.2) | 3.15–3.41 (*m*) | – | 171.8 |
| Equiv. PhOH | $\delta(CHCO_2)$ | $\delta(CH_2N)$ | $\delta$(C=N or O–C–N) | $\delta(CO_2)$ |
| 0.5 | 3.93 (*dd*, *J* = 9.1, 3.8) | 2.56–2.62 (*m*), 2.42–2.50 (*m*) | – | 176.2 |
| 1 | 4.18 (*dd*, *J* = 9.0, 3.1) | 2.77 (br. *t*, *J* = 6.5) | – | 174.5 |
| 3 | 4.62 (br. *d*, *J* = 8.2) | 3.37–3.44 (*m*), 3.04 (*dt*, *J* = 13.4, 8.6) | 188.8 | 171.6 |
| 6 | 4.47 (br. *d*, *J* = 7.6) | 3.25–3.40 (br. *m*), 2.57–2.80 (br. *m*) | 191.1 | 172.3 |
| 6 (dil)[a]) | 4.47 (br. *d*, *J* = 6.7) | 3.24–3.38 (br. *m*), 2.58–2.80 (br. *m*) | 191.2 | 172.5 |
| Equiv. HFIP | $\delta(CHCO_2)$ | $\delta(CH_2N)$ | $\delta$(C=N or O–C–N) | $\delta(CO_2)$ |
| 0.5 | 3.79 (*dd*, *J* = 9.4, 4.4) | 2.52 (*ddd*, *J* = 9.3, 5.4, 3.2), 2.34 (*td*, *J* = 9.5, 7.0) | – | 176.6 |
| 1 | 3.96 (*dd*, *J* = 9.2, 3.8) | 2.55–2.68 (*m*) | – | 175.2 |
| 3 | 4.38 (*d*, *J* = 7.8) | 3.40 (*ddd*, *J*= 11.6, 8.4, 1.8), 2.88 (*dt*, *J* = 13.9, 8.6) | 188.1 (trace) | 170.9 |
| 6 | 4.29 (*d*, *J* = 7.2) | 3.40–3.55 (*m*), 2.65 (*dt*, *J* = 13.1, 8.2) | 191.2 | 171.4 |

[a]) Diluted from a 0.7M to 0.3M solution.

additive in $C_6D_6$ (see especially the $^{13}C$ signal near 190 ppm for PhOH and HFIP in *Table 3*)[29]). Interestingly, LiBr in THF also leads to the opening of the 'lactone' ring of oxazolidinone **8** to give what might be called a $Li^+/Br^-$-neutralized zwitterion **17c**. In the ROD solvents, there is NMR evidence for H/D exchange in the six-membered ring of **17**: in the $^{13}C$-NMR spectrum, two of the signals (36.7 and 37.1 ppm) attributed to $CH_2$ groups show broadening, and integration of the *multiplet*s originating from the $CH_2$ groups in 3-, 4-, 2′-, 3′-, 4′-, 5′-, and 6′-positions indicates missing H-atoms. This observation is compatible with an equilibrium between the zwitterion and an enamine derivative (*Table 4*).

Table 4. *H/D Exchange in the Iminium Carboxylic Acids/Iminium Carboxylates* **17** *in Deuterated Solvents* (*cf. Table 2*). $^1H$ Loss was determined by integrating the upfield $^1H$ multiplets (all H-atoms except of $CH_2N$, and CHN) and subtracting the number obtained from the expected value. These measurements were performed with the same type of NMR instrument and the same settings. While the numbers should not be taken as relative rates, it appears to be safe to say that H/D exchange is fastest in the least acidic solvent, *i.e.*, MeOD.




**17**

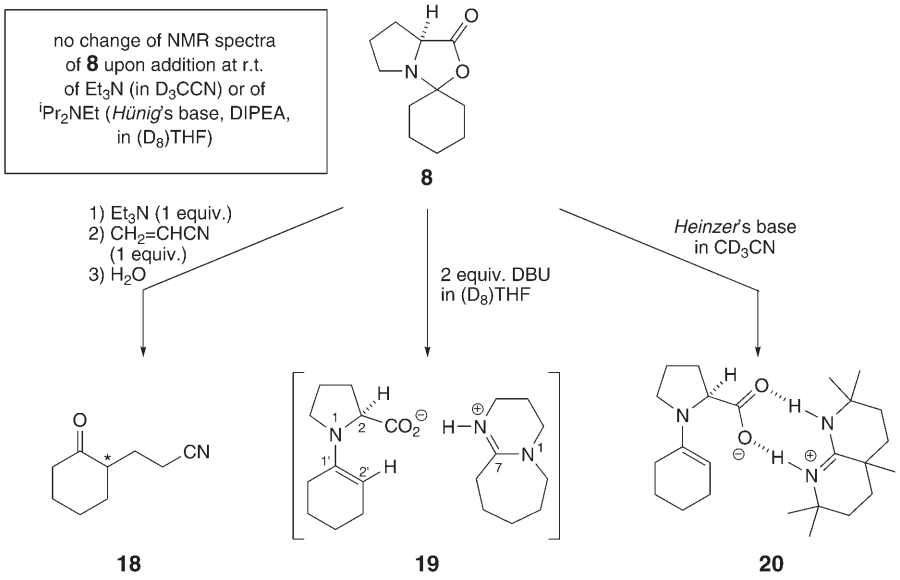
| Solvent | $CD_3OD$ | $C_6D_5OD$[a]) | $(D_2)$HFIP | $D_3CCO_2D$[b]) | $F_3CCO_2D$ |
|---|---|---|---|---|---|
| Time | < 10 min | 4 h | 40 min | 3.5 h | 3.5 h |
| H loss | 3.2 | 0.9 | 0.7 | 1.3 | 2.4 |

[a]) NMR Measurements were performed at 50° to ensure that the solvent would be a fluid liquid. [b]) In this case, a residual solvent peak (2.04 ppm) could be present amongst the *multiplet*s being integrated, and thus the value obtained for proton loss would be an underestimate.

We then treated solutions in dry $CD_3CN$ or $(D_8)$THF of the oxazolidinone **8** at + 20° with equimolar amounts of increasingly strong bases. No NMR- or IR-detectable changes occurred with $Et_3N$ or *Hünig*'s base, although both catalyze reactions of **8** with electrophiles (*vide supra*, *Sect. 3*, and formation of the *Michael* adduct **18** to acrylonitrile in *Scheme 8*, below). With the stronger amidine bases DBU and 3,3,6,9,9-pentamethyl-2,10-diazabicyclo[4.4.0]dec-1-en (*Heinzer*'s base [13]), the characteristic spectroscopic features of the oxazolidinone completely disappear: with DBU in THF the oxazolidinone C=O absorption at 1770 $cm^{-1}$ disappears, and in the

[29]) Strikingly, the C=O C-atoms of **8** and of the ring-opened species **17** have very similar $^{13}C$-NMR chemical shifts (172 – 177 ppm).

Scheme 8. *Reactions of Spiro-oxazolidinone* **8** *with Bases, and Identification and Isolation of the Enamino Carboxylate Salts* **19** *and* **20**, *Respectively.* While $Et_3N$ alone does not detectably open the 'lactone' ring (NMR measurement after 3 days in $CD_3CN$ at r.t.), it does catalyze addition to acrylonitrile to give enantiomerically enriched keto nitrile **18** (for details, see *Exper. Part*).




$^{13}$C-NMR spectrum ((D$_8$)THF) new peaks are present, which are compatible with the enamino-carboxylate **19**: 179.0 (R–$CO_2$), 143.4 (C(1′)), and 89.9 ppm (C(2′)). There is also the signal originating from the bridgehead C-atom C(7) of protonated DBU at $\delta$ 164.3 ppm.

With *Heinzer*'s base, which, upon protonation, becomes an ideal cationic counterion[30]) of a carboxylate anion [13], an instantaneous reaction takes place in MeCN, and the extremely hygroscopic salt **20** of the enaminocarboxylate is isolated (85% after non-aqueous workup and recrystallization from $C_6H_6$ in a dry box). In the $^1$H-NMR spectrum ($CD_3CN$) of **20**, there is a *triplet* at $\delta$ 3.9 ppm from the vinylic H-atom of the enamino group (*cf.* the spectra of the enamines formed from proline *tert*-butyl ester [37] or pyrrolidine and cyclohexanone; see *Scheme 4*, *Fig. 1*,*a*, and the corresponding *Exper. Part*).

In summary, we have shown that the 'neutral' oxazolidinone from proline and cyclohexanone is converted to an iminium-carboxylic acid or a betaine in protic media (also with LiBr in THF), and to an enamino-carboxylate with bases, and we have been

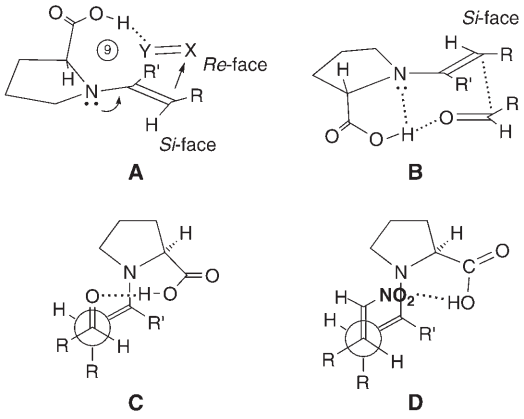
30) The salt **20** was found to be sensitive to moisture. The even more basic analogous guanidine base (*Schmidchen*'s base, not known at the time) might lead to a less hygroscopic salt [33e].

able to isolate and fully characterize a salt of the elusive enamino-carboxylic acid derived from a ketone and proline[31]).

**6. Mechanistic Models of Proline Catalysis.** – 6.1. *The Commonly Accepted Catalytic Cycle.* There is agreement in the 'community of organocatalysis' that the sequence of events in proline-mediated reactions of aldehydes and ketones with electrophiles [3][5][6b] is as depicted in *Scheme 9*. In this catalytic cycle, the oxazolidinones are involved in 'parasitic' [5] equilibria and do not play any role in the stereochemical course of the reactions. Besides the 'parasitic' species, which had been seen before, we have now characterized the assumed intermediates of this catalytic cycle, namely the iminium and the enamine species.

6.2. *Aspects of the Current Mechanistic Model.*

*i*) The generally accepted model for the coupling between the nucleophilic enamine C-atom and an electrophile is depicted in **A** [3][6b]. As we understand it, the predominant structural factor that determines stereoselectivity (in, for instance, an aldol addition) is assumed, in this model, to be the activation of the electrophilic reactant by an intramolecular H-bond between proline's COOH group and the carbonyl O-atom of an aldehyde in a nine-membered H-bonded ring[32]). A second determinant is the s-*trans*-arrangement of the enamine C=C bond relative to the position of the COOH group.




*Re*/*Re*-coupling of trigonal centers

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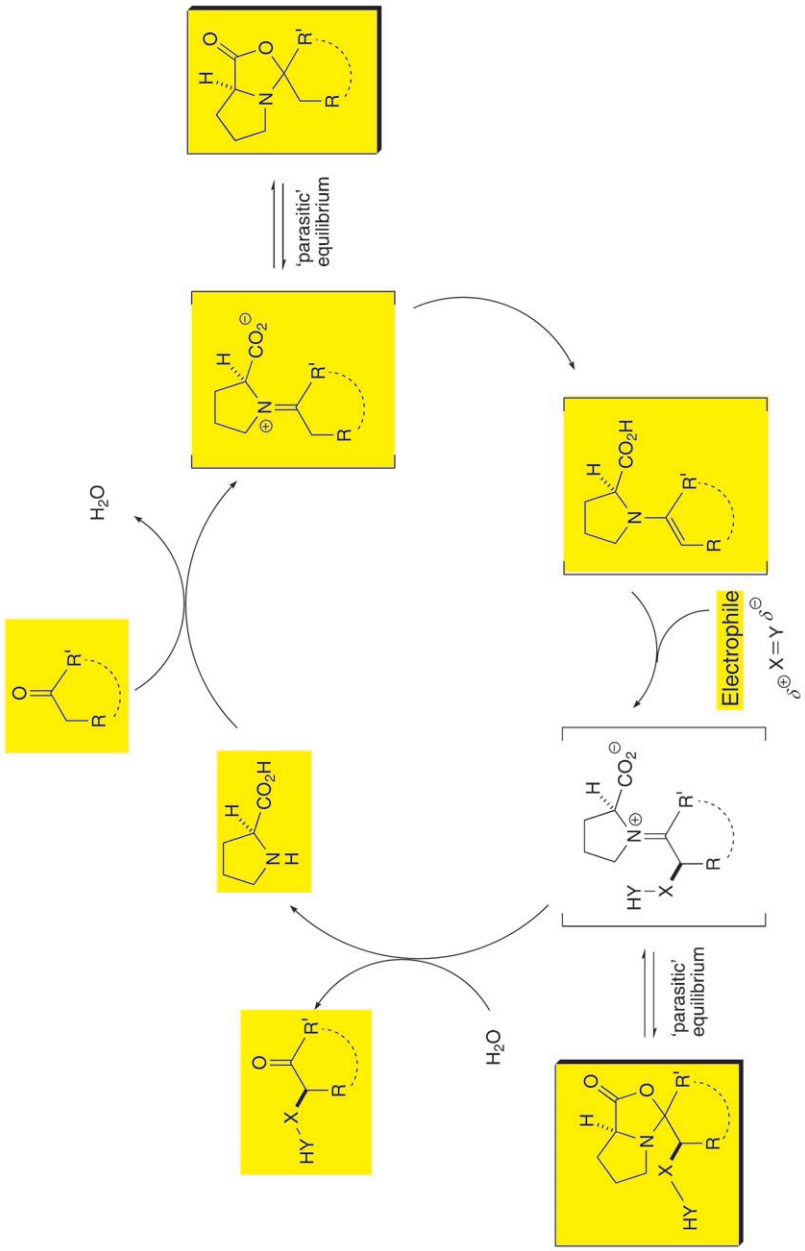
31) Cationic, *i.e.*, *protonated* species involved in the catalytic cycle (acetone + aldehydes + proline) have very recently been intercepted and characterized by mass spectrometry (ESI-MS/MS) [42].

32) In the case of $\beta$-nitrostyrene as electrophile X = Y (**A**; *cf.* **D**) an eleven-membered H-bonded ring has been depicted [27a]. The same is true for nitronate or malonate *Michael* additions to enones (Scheme 15 in [3a]).




Scheme 9. *The Catalytic Cycle of Proline-Catalyzed Reactions* (of aldehydes and ketones with electrophiles), *in which Oxazolidinones Play the Role of 'Parasitic' Species Not Involved in Any Product or Reactive-Intermediate-Forming Steps* [3c][5]. All the species marked in yellow have now been characterized by the spectroscopic studies reported herein, and by the investigations of the *List* and *Blackmond* groups (see *Sects. 3–5*).

*ii*) The s-*trans*-conformation of the COOH group is used for electrophile activation[33]).

*iii*) We agree with *Houk* and co-workers that the originally invoked H-bond formation to the enamine N-atom (*cf.* **B**) that is still widely depicted in recent publications, should be abandoned [3c][6b][34]).

*iv*) The relative topicity of addition to the enamine C=C bond follows the topicity rule for the coupling of trigonal centers [45] as shown for the aldol addition in **C** and for the *Michael* addition in **D**, which invariably[35]) occur with relative topicity *lk* (*Re*/*Re*).

*v*) There is another aspect of the commonly accepted mechanism of proline catalysis: unsymmetrical ketones, in the simplest case butan-2-one, are reported to give products of reactions with electrophiles only on the higher-substituted $\alpha$-C-atom (*Scheme 10*)[36])[37]). To the best of our knowledge, this *regioselectivity* is not commented on in mechanistic discussions of the reactions, apart from general statements such as '*the higher-substituted enamine is more reactive*' [3][5][38]).

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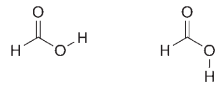
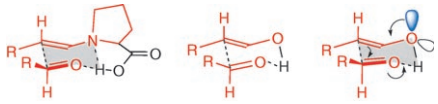
[33]) The s-*cis*-form of a carboxylic acid is more stable (and less acidic) than the s-*trans*-form (see *Formulae* in this footnote). In the case of HCOOH (least steric hindrance in the s-*trans*-form), the difference, by which s-*cis*-form is more stable, is 3.5 kcal/mol [43].



s-*cis* s-*trans*

[34]) Originally, this H-bridge to the enamine N-atom has been formulated in analogy to the *Zimmerman – Traxler* [44] formulation of the chair-like aldolization transition state, in which a metal ion or the enol H-atom is bridging the two O-centers of the reactants [3a]. Interestingly, this analogy is intrinsically false, since the bridged enamine N-atom lacks the additional lone pair that would be required for the analogy to hold. In the *Zimmerman – Traxler* aldolization transition state it is a *non-bonded* lone pair of the complexed enolate O-atom, from which the ensuing $\pi$-bond of the aldolization product's C=O group is generated.



[35]) We found only one exception to this rule: additions of aliphatic aldehydes to nitro-olefins have been reported to give products of *Si*/*Si* coupling under proline catalysis (with poor enantioselectivities [31][46]; *cf.* also *Footnote 56*).

[36]) The *Hajos – Wiechert* intramolecular aldol addition [6b][11][12] is an obvious exception; a four-membered ring would be formed if reaction took place at the higher-substituted $\alpha$-C-atom.

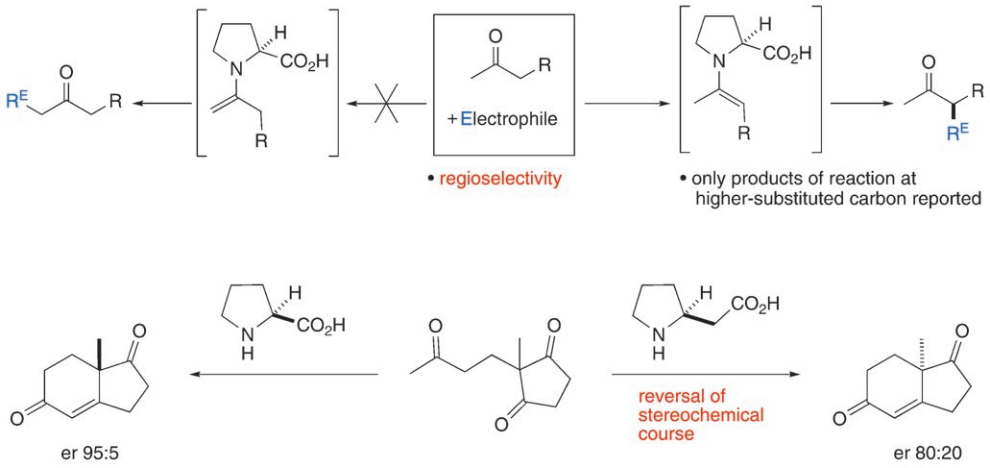
[37]) We are aware of only one report in which butan-2-one and hexan-2-one were added to $\beta$-nitrostyrene, with (*S*)-$\beta$-homoproline as the catalyst, to give mixtures of constitutional isomers; the reaction was carried out with a molar ratio of $\beta$-nitrostyrene/$\beta$-homoproline · HCl/$Et_3N$ 1:0.2:0.2, in *t*-BuOH as the solvent [47].

[38]) Enamines are known to equilibrate with their less stable regioisomers and give constitutionally isomeric products, depending on the electrophile employed [48 – 50]; thus the enamine from $\beta$-tetralone and pyrrolidine or 2-(methoxymethyl)pyrrolidine can give rise to products which are substituted in the 1- or in the 3-position of the tetralone skeleton [29c].

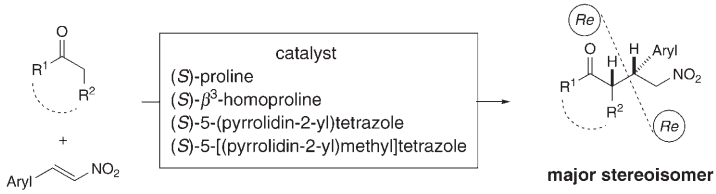
*vi*) From the early days of proline catalysis, it is known that the stereochemical course of reactions may reverse when (*S*)-proline is replaced by (*S*)-*β*-homoproline ((pyrrolidin-2-yl)acetic acid) [51][52a] (see *Scheme 10* for the *Hajos–Wiechert* reaction[39]). With one exception [52b], this puzzling observation has not found rationalization attempts in the literature.

*vii*) Note that *N*-alkyl amino acids other than proline, including azetidine- and piperidine-2-carboxylic acid, are generally not nearly as good catalysts[40][41]; the yields of *intra*- and *inter*molecular aldol additions catalyzed by *N*-methyl amino acids are low, and the enantioselectivities are poor, often *ca.* 50:50 [3c][54].

*Scheme 10*




[39]) Besides the *Hajos–Wiechert* reaction, only the *Michael* addition of ketones to *β*-nitrostyrenes appears to have been tested with homoproline [47] and with the homologue of pyrrolidyl-tetrazole [36b][53b]:




In all cases the major stereoisomer has (2*S*,1′*R*)-configuration. The addition of acetone to 4-nitrobenzaldehyde was not catalyzed by homoproline at all [51]. Thus, it is not possible, at this point, to draw any general conclusions, and it is not worthwhile to speculate about a mechanistic model for homoproline catalysis in the absence of further experimental results.

[40]) Monocyclic oxazolidinones from *N*-alkyl amino acids do not provide sterically distinct *endo*/*exo*-spaces (see *Sect. 7.1*).

[41]) For conditions under which simple proteinogenic amino acids catalyze aldol additions of ketones (mainly cyclohexanone and 2,2-dimethyl-1,3-dioxan-5-one) to aromatic aldehydes, see [54b].

**7. Are Oxazolidinones Product-Determining Species?** – Although they are the only IR- and NMR-detectable species in the course of proline-mediated transformations, oxazolidinones play no role in the discussions of mechanistic models of these reactions, other than being temporary 'parasitic products of collapse' of intermediate zwitterionic iminium-carboxylates (see *Sect. 6* and *Scheme 9*). We now address the question posed in the title of the present paper, more specifically the question, whether oxazolidinones may be involved in the regio- and stereochemical course of proline-catalyzed reactions. To approach this issue, a detailed stereochemical analysis of oxazolidinone structures is warranted.

7.1. *Structures of Oxazolidinones.* Inspection of the structures of bi- and tricyclic oxazolidinones (*Fig. 5*) reveals the following facts: the oxazolidinones derived from aldehydes are more stable with the substituent at C(2) in the *exo*-position, in non-symmetrical ketone derivatives the larger substituent will prefer to reside in the *exo*-position, and in oxazolidinones derived from symmetrical ketones the substituent in the *exo*-position is less sterically hindered (*Fig. 5*,*a* and *b*)[42]). Furthermore, in the spirocyclic cyclohexanone-derived oxazolidinone **8**, the conformer with axial O-atom and equatorial N-atom has to be assumed to be more stable than the conformer with the two heteroatoms reversed[43]) (*Fig. 5*,*b*).

A search in the *Cambridge Crystallographic Database* reveals the following facts about proline-derived oxazolidinone structures[44]) (*Fig. 6*): their oxa-aza-bicyclo[3.3.0]octane skeletons are bent in a dish-like shape with distinct *exo*- and *endo*-faces; the N-atom pyramidalisation (distance of the N-atom from the plane of its three bonding partners) is *ca.* 0.5 Å ($sp^3$-N) [9][56]; the *virtual* dihedral angle, which the N-atom lone pair (lp) forms with the neighboring C–O bond, lp–N–C–O is *ca.* 110° (*cf. Fig. 5*,*c*, left-hand side, and *Fig. 6*,*b*); the average values of the C–O, C=O, and C–N bond lengths are *ca.* 1.45, 1.20, and 1.45 Å, respectively (*Fig. 6*,*a*); comparison with the structures of analogous bicyclic lactones (3-oxabicyclo[3.3.0]octan-2-ones)[45]) shows that both the C–O and the C=O bond lengths (*ca.* 1.45 and 1.20 Å, resp.; *Fig. 6*,*c*) are essentially identical to those in the oxazolidinones; this is as surprising as it is important: no stereoelectronic effect of the N-atom or its lone pair on the oxazolidinone structure is discernible; this is compatible with the virtual lp–N–C–O dihedral angle of *ca.* 110°, and furthermore compatible with the fact that the C=O bands in the IR spectra of the oxazolidinones (**2** and **8**) are near 1770 $cm^{-1}$, a typical value for $\gamma$-lactones. For a 'dissociative' ring-opening of an oxazolidinone to a zwitterionic iminium carboxylate (*Fig. 5*,*d*), a process that formally does not follow a

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[42]) All pivalaldehyde derivatives have exclusively *exo*-configuration [16–19][55], so has the chloral derivative of proline [7]. In oxazolidinones derived from aldehydes RCHO with smaller R groups, NMR-detectable amounts of a minor diastereoisomer have been reported ([8] and hitherto unpublished results by *W. Prikoszovich*, *B. Linder*, *Novartis Pharma AG*, Basel).

[43]) The NMR spectrum of **8** does not contain any signals arising from a second conformer: although no detailed 2D-NMR measurements have been carried out, we tentatively assign the conformation with the axial O-atom and equatorial N-atom to the one and only detectable form of **8** (*Fig. 5*,*b*).

[44]) As of September 15, 2006 there were seven X-ray structures with altogether twelve independent oxazolidinone molecules of this type in the file: CALJOO, HEKQOD, KATMUN, VACKUG, YALYEQ, YANDAT, ICOQIB (*cf. Fig. 6*,*a* and *b*).

[45]) The *Cambridge* file codes of 18 independent lactone structures of this type are shown in *Fig. 6*,*c*.

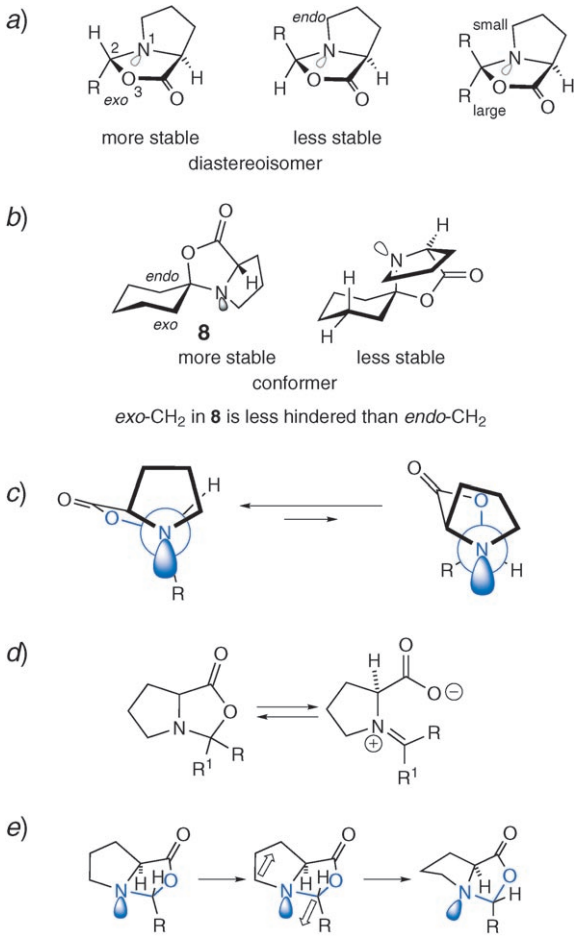


Fig. 5. *Structures of oxazolidinones derived from proline. a*) In aldehyde derivatives, the R group is preferentially in the *exo*-position, and the larger group of unsymmetrical ketones R–CO–R′ resides on the *exo*-face of the bicyclo[3.3.0]octane skeleton; *b*) the *exo*-substituent of symmetrical ketones RCOR is less hindered than the *endo*-substituent, and in **8** the position of the O-atom is expected to be axial, and that of the N-atom equatorial; *c*) there is no lone-pair–(C–O) interaction in the most stable conformation of a bicyclic oxazolidinone; the conformation with such an interaction will be more strained. (*cf. e*); *d*) dissociative ring opening/closure of a bicyclic oxazolidinone; *e*) distortion of the more stable conformer to a more strained conformer with lone pair$_N \rightarrow \sigma^*_{C-O}$ interaction.

*Bürgi–Dunitz* trajectory [57][46]), the ideal conformation would have the N-atom lone-pair and the C–O bond to be cleaved in an *antiperiplanar* orientation; such a

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[46]) In the *Baldwin* terminology, the closure of this zwitterion to the oxazolidinone would be called a disfavored 5-*endo-trig* process [58]. Factors stronger than stereoelectronic effects come into play in the formation or collapse of a zwitterion (*cf.* the formation of oxazolidinones and imidazolidinones from their imino-caboxylate and imino-amide precursors, resp. [21]).

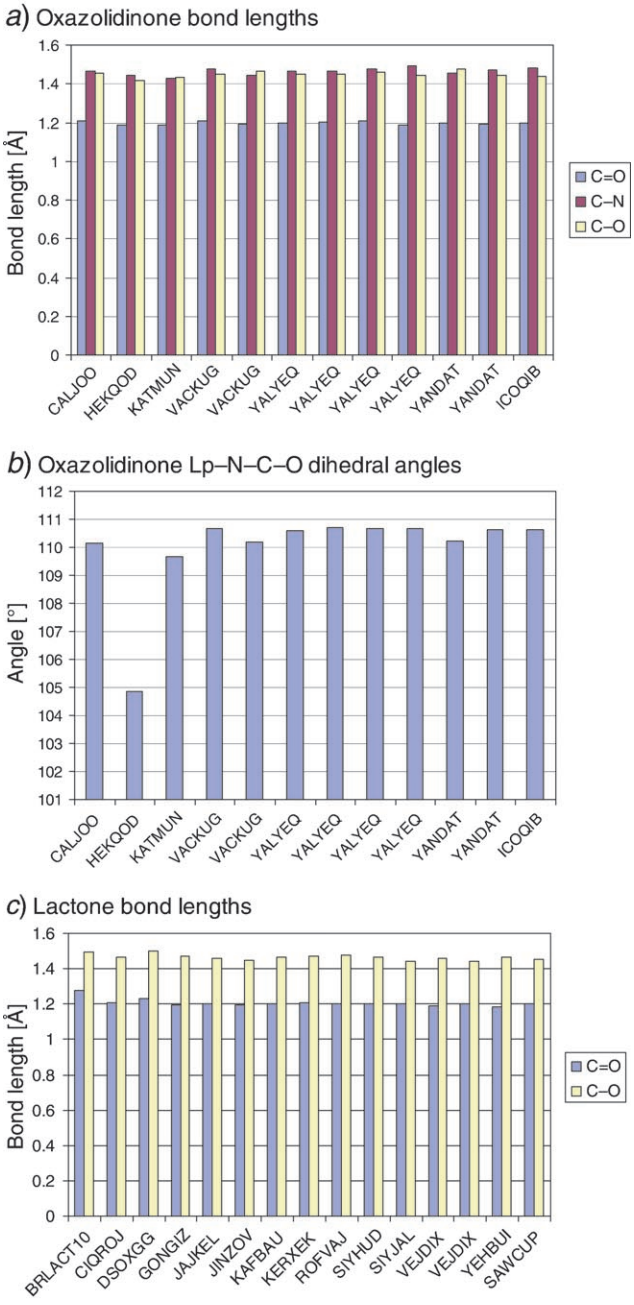


Fig. 6. *Comparison of oxazolidinones and lactones with bicyclo[3.3.0]octane skeletons in crystal structures. a*) C=O, C–N, and C–O bond lengths in oxazolidinones; *b*) virtual (lone-pair)–N–C–O dihedral angles in oxazolidinones (*cf. Fig. 5*, *c*, left-hand side); *c*) C=O and C–O bond lengths in bicyclic lactones are essentially identical to those in oxazolidinones (*cf. a*). Data from the *Cambridge Crystallographic Database* as of September 2006.

conformation[47]) (*Fig. 5,c*, right-hand side, and *Fig. 5,e*) has both five-membered rings in extreme envelope shapes and must be assumed to be strained, compared to the stable conformer seen in the crystal structures, in which the N-atom lone pair and the reacting bond are at an angle close to 120° in an almost ideally eclipsed conformation (*Fig. 5,c*, left-hand side, and *Fig. 6,b*). In this connection, the very fact that oxazolidinones such as **8** can be isolated and even distilled seems relevant. The same is true for the observation that **8** is not seen to react in THF at low temperature with strong electrophiles (such as $\beta$-nitrostyrene), but does so in the absence of base at room temperature (see *Scheme 5* and *Table 1*).

7.2. *A Possible Oxazolidinone Route for Proline Catalysis.* Assuming that the bond cleavage would occur, indeed, from the strained, but stereoelectronically reactive conformation[47]) of an oxazolidinone, with the more stable arrangement of the larger substituent in the *exo*-position, *this substituent and the C-atom bearing the carboxylate group will end up in the (*Z*)-position on the iminium C=N bond of the resulting zwitterion* (*Scheme 11*). Subsequent intramolecular proton transfer from the $\alpha$-C=N$^{\oplus}$ C-atom to the carboxylate anion would give rise to the isomeric, neutral enamino-carboxylic acid, with the C=C bond of (*E*)-configuration and the C-atom bearing the COOH group in an s-*cis*-arrangement with the enamino C=C bond. In such a scenario, the regio- and stereochemical course of the enamine formation would be coupled to the *exo*-preference of substituents on the bicyclic oxazolidinones. For the analogous enamino-carboxylic acid formation from the tricyclic oxazolidinone derivative **8** of cyclohexanone, see *Scheme 12*.

The proline-catalyzed reaction of aldehydes and ketones with electrophiles is a process that, according to experiments, invariably[35]) occurs from the trigonal *Re*-face of the intermediate enamine. In accordance with this fact, as well as based on our observation that base catalyzes the reaction of an oxazolidinone with electrophiles[48]), we consider that, after deprotonation of the COOH group to the carboxylate, the C,C-bond-forming reaction occurs as a *trans*-addition to the enamino C=C bond in its s-*cis*-arrangement, with concerted regeneration of an oxazolidinone ring (*Schemes 11* and *12*). This would provide a product with the correct configuration of the newly formed stereogenic center and with the large group in the *exo*-position. Furthermore, in such a reaction mode, the electrophile would approach the substrate from the side that is unhindered by the carboxylate group and, from the final product's (the oxazolidinone's) point of view, correspond to the approach from the sterically freely accessible *exo*-half-space of the ensuing bicyclo[3.3.0]octane ring system.

As the barrier to rotation around the C=C–N single bond is assumed to be low [9][59], equilibration between the s-*cis*- and s-*trans*-forms[49]) of the enamino-

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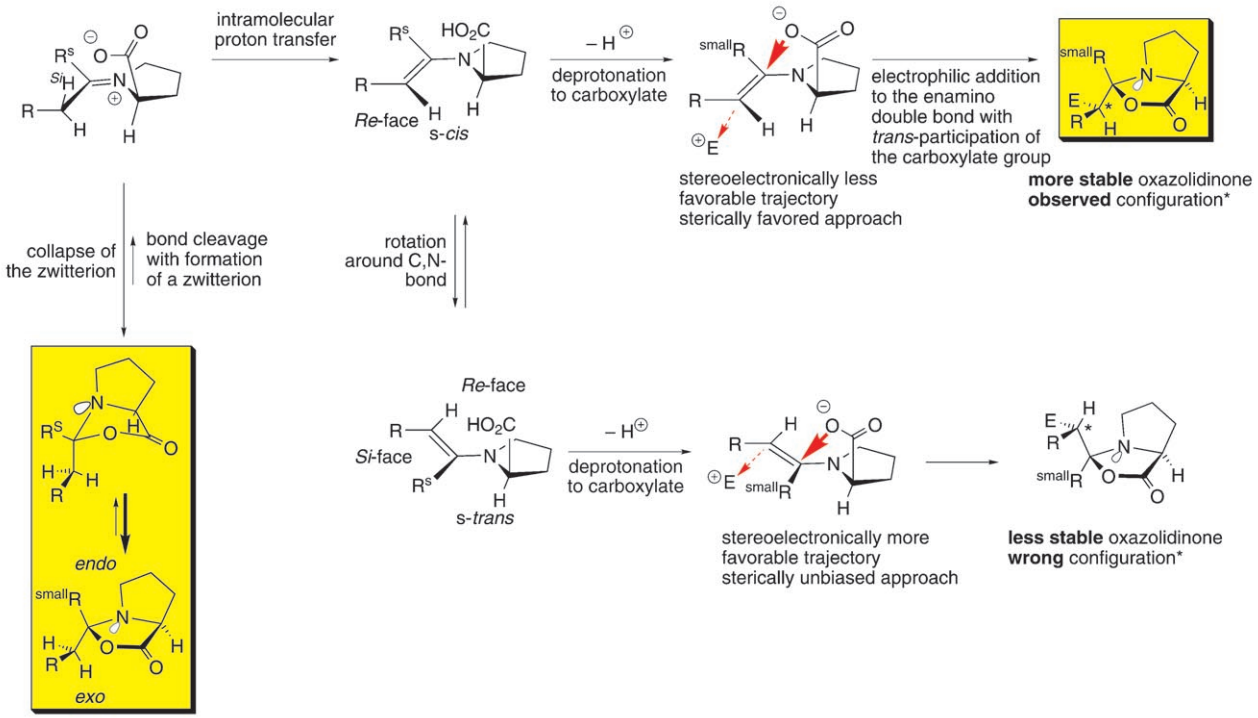
47) We here use the term 'conformation' rather than 'conformer', because the arrangement around the N–C bond with antiperiplaner lone-pair and O-leaving group may actually not be an energy minimum but a point on the way to the transition state of C,O-bond cleavage in the dissociative process (*Scheme 11*) and in the eliminative process (*Scheme 13*).

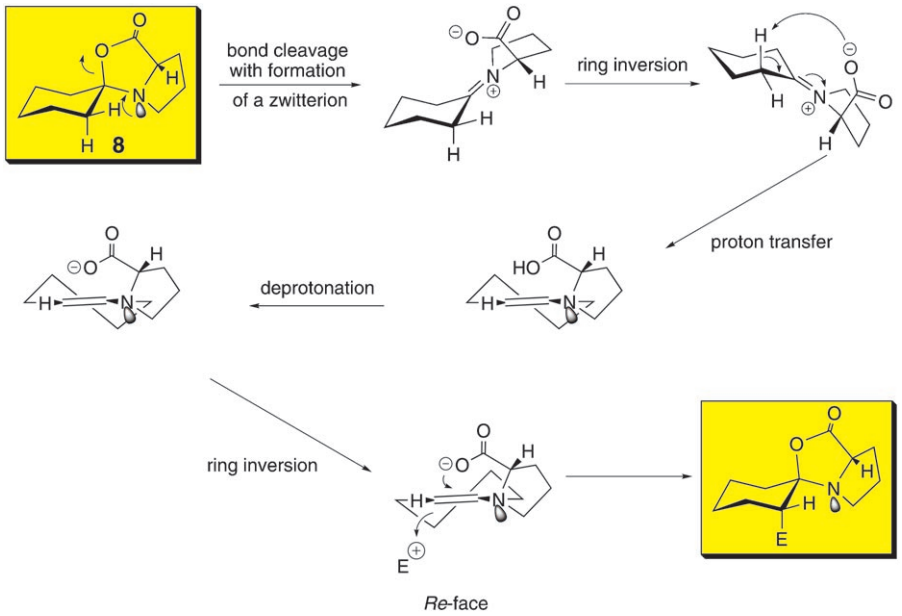
48) For simplicity, we use an E$^{\oplus}$ for the electrophile, rather than an E$\delta^{\oplus}$ in *Schemes 11–13*.

49) This is the structure of the enamino-carboxylic acid proposed in the commonly accepted mechanism; see **A**–**D**.

Scheme 11. *Regio- and Stereoselectivity of Reactions between an Electrophile and a Proline Derivative of an Unsymmetrical Ketone Interpreted in Terms of the* exo/endo-*Bias for Substituents on the Oxazolidinone Skeleton. Top:* the C–O bond (in the strained conformation shown in *Fig. 5*, *c*, right-hand side) dissociates to a zwitterion of (*Z*)-configuration around the N=C bond; proton transfer (→(*E*)-enamino double bond in an s-*cis*-conformation), deprotonation and *trans*-addition of $CO_2^{\ominus}$ and $E^{\oplus}$ generate a product oxazolidinone with the larger substituent in *exo*-position and with the observed absolute configuration of the newly created stereogenic center. *Bottom:* the s-*trans*-conformation of the enamino carboxylate would lead to an oxazolidinone with the larger substituent of opposite configuration in the *endo*-position.



Scheme 12. *Reaction of the Tricyclic Spiro-oxazolidinone* **8** *with an Electrophile in Analogy to the Process Outlined in* Scheme 11 *for an Unsymmetrical Ketone Derivative*

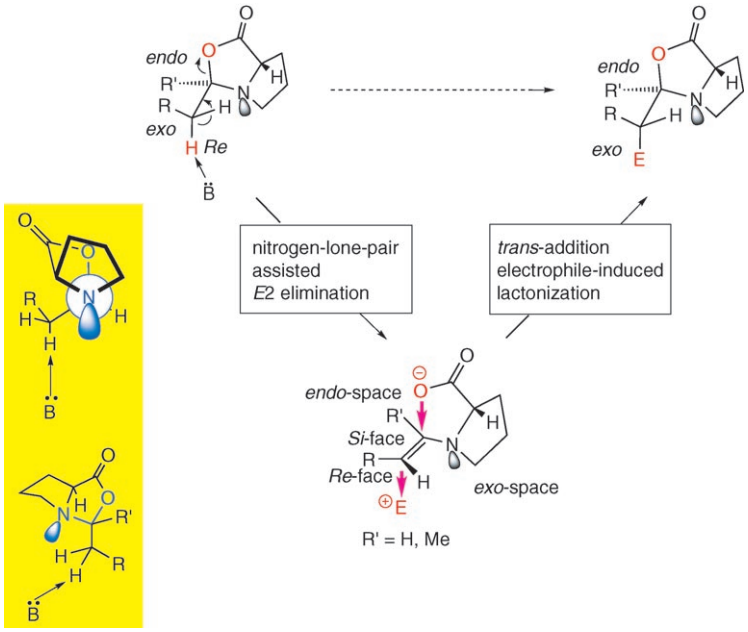



carboxylic acid will occur readily (see *Scheme 11*). Note that the trajectory for the *trans*-addition with this s-*trans*-form of the enamino-carboxylate (*Scheme 11*, bottom) would be expected to be stereoelectronically more favorable, but would lead to an oxazolidinone with the larger group in the *endo*-position, and, worse: with the *wrong* configuration of the newly formed exocyclic stereogenic center.

The course of this reaction, as described above, would consist of the following elementary steps: a heterolytic or $S_N1$-type bond dissociation with formation of an iminium-carboxylate, an *intra*molecular proton transfer creating the enamine C=C bond, an *inter*molecular deprotonation of the COOH group, and, finally, a concerted *trans*-addition of the electrophile and the carboxylate group to that enamine C=C bond in its s-*cis*-conformation, to form an oxazolidinone ring. A weakness of this sequence of events is the mechanistic asymmetry between the process that opens the oxazolidinone ring and the process that closes it. The alternative for the ring opening that would be symmetric to the carboxylate-assisted addition of the electrophile to the enamino C=C bond, would be a concerted *E*2-type opening of the oxazolidinone ring by base, leading directly to the enamino-carboxylate and circumventing the iminium intermediate. Such a concerted elimination would (formally) have to start from the strained oxazolidinone conformation[47]), in order to offer, for the ensuing enamino C=C bond, optimal assistance by the lone pair (see *Scheme 13*).

There is an intriguing stereochemical difference between the bond-dissociation and the *E*2-elimination route: in the former process, the diastereotopic H-atom $H^{Si}$, in the

Scheme 13. E2-*Elimination Step to the Enamino Carboxylate Shown in* Scheme 11 (*top*). Instead of a bond dissociation in the strained conformer followed by deprotonation, the precursor for the *trans*-addition with 'lactonization' would be formed directly by the action of an external base in this alternative mode.

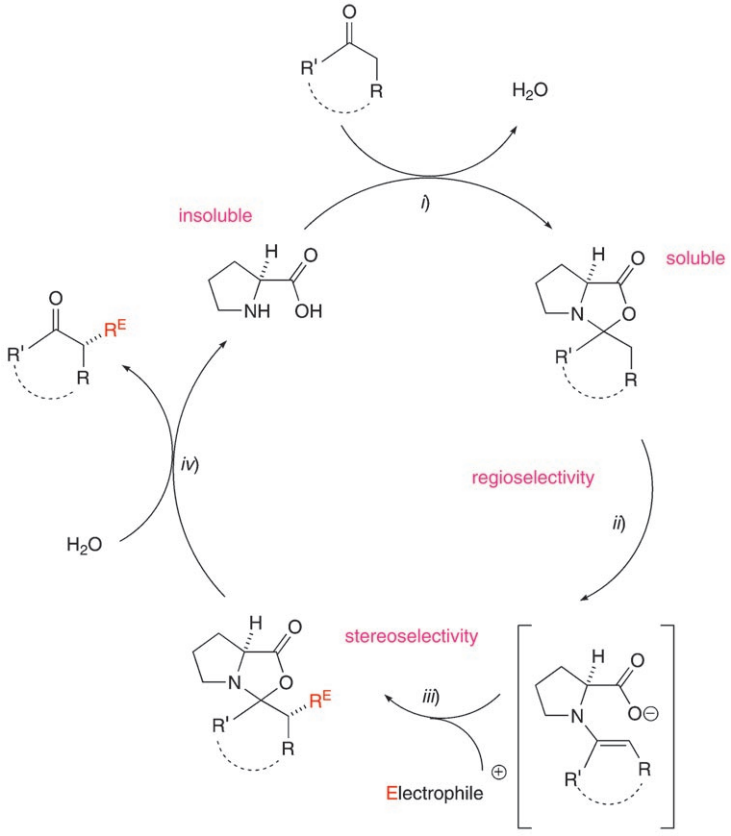



latter $H^{Re}$, would be removed by the *intra*- and the *inter*molecularly acting base, respectively (*cf. Schemes 11–13*). These different stereochemical outcomes could, in principle, be probed by experiments with D-labelled compounds.

Seen from the vantage point of this discussion, oxazolidinones, rather than being 'parasitic' species, would play a decisive role in determining the stereochemical course of events of proline-catalyzed reactions. In this alternative mechanistic model, the underlying product-determining factor is steric in nature, in the sense that the observed steric course leads to the more stable oxazolidinone carrying the larger substituent in the sterically less hindered *exo*-position of the bicyclo[3.3.0]octane system. Such a view implies that the factor, which is responsible for the difference in the product stability of the two diastereoisomers, is already active in the corresponding diastereomorphic transition states. The catalytic cycle for proline-mediated reactions of aldehydes and ketones with electrophiles, where oxazolidinones play a pivotal role, is depicted in *Scheme 14*.

The commonly accepted key step is replaced by an electrophilically induced $\gamma$-lactonization step (*Schemes 11–14*). Such a view implies a conformational pre-organisation of the four reaction centers, especially the carboxylate group relative to the enamine C=C bond. The type of reaction proposed to take place is well-known to

Scheme 14. *The Proline Catalytic Cycle with a Pivotal Role of Oxazolidinones* (*cf.* the Catalytic Cycle with 'Parasitic' Oxazolidinones in *Scheme 9*). The 'oxazolidinone route' consists of the four steps: *i*) formation of the oxazolidinone (a proline derivative, which has good solubility in organic solvents) in a kind of dehydrating acetalization or ketalization; *ii*) opening of the oxazolidinone ring with regioselective formation of the enamino moiety in two steps (*Scheme 11*) or in one step (*Scheme 13*); *iii*) *trans*-addition to the enamino double bond in an electrophile-induced $\gamma$-lactonization, setting the configuration of the new stereogenic center in the *exo*-space of the product oxazolidinone (*cf. Scheme 11*, *top*); *iv*) hydrolytic cleavage of the product oxazolidinone.




occur fast and selectively in proto-lactonizations [60a], halo-lactonizations, or thio- and seleno-lactonizations [60b] of unsaturated carboxylic acids[50]).

What we lose in the oxazolidinone route, relative to the *List–Houk* model [3a][3c][5][6b], is the *intramolecular Brønsted*-acid activation of the incoming

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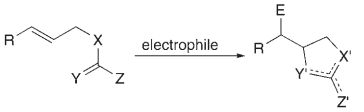
[50]) Similar processes occur with unsaturated carbonates, carbamates, and imidates, with formation of the corresponding heterocycles [61].

| X | O | O | NH | NR | NR | O |
|---|---|---|---|---|---|---|
| Y | O | NH | O | O | NH | NH |
| Z | $O^{\ominus}$ | $CCl_3$ | $CCl_3$ | OBn | OEt | $NR_2$ |



electrophile (see **A**–**D**)[51]). We imply that this H-atom can be supplied by the environment (*cf.* the role of $H_2O$ in proline-catalyzed reactions [54b][62] and the excess proline (sometimes >100%) present under the commonly employed conditions [3][52])). Another question concerns the base which would have to deprotonate the COOH group (*Schemes 11* and *12*) or cause *E*2-type elimination (*Scheme 13*). As suggested in *Sect. 3* above, the base could be an oxazolidinone itself, or a product formed with an electrophile (*cf.* the autocatalytic effects discussed in *Sect. 4*), or, again, proline[52]). We should also remember that the intermolecular proline-catalyzed transformations are often slow at room temperature (reaction times of up to 40 days have been reported), and that many require large excesses of reagent (for instance, of ketone which is sometimes used as the solvent) [3]. It is finally interesting to note at this point that certain proline-catalyzed reactions are carried out in the presence of $HClO_4$, and that in others a Li or a Rb salt of proline is employed rather than the free amino acid [3].

**8. Other Reactions of Proline-Derived Enamines with Electrophiles.** – Both, the *List*–*Houk* model, and the model we discuss in the present paper for proline-catalyzed aldolizations, and other reactions of aldehydes and ketones with electrophiles require, as a mechanistically crucial functionality, the free COOH group of the catalyst. There exists, however, a large body of experimental studies on the stereochemical course of reactions proceeding *via* enamines derived from *homochiral* proline derivatives that lack this COOH function and contain, instead, other substituents at the corresponding position of the pyrrolidine ring.

8.1. *Stoichiometric Use of Enamines.* In a pioneering work dating back to 1969, *Yamada et al.* have used pyrrolidine enamines prepared from carbonyl compounds and L-proline esters and amides in *stoichiometric* reactions with electrophiles [37]; the stereochemical course of all these enamine reactions followed the same rule as the L-proline-*catalyzed* reactions of aldehydes and ketones: *the product-determining attack of the electrophile at the enamine C=C bond occurs preferentially from the* Re*-face of the trigonal center*. The same holds for *Michael* additions of enamines, prepared from prolinol methyl ether[53]) and cyclic ketones, to nitro-olefins or benzylidene malonates [29], and for *Mannich* reactions with iminium salts [64]; remarkably, this stereochemical preference was observed even in the addition to β-nitrostyrene of the analogous 2-propylpyrrolidino derivative (containing no heteroatom in the side chain!)

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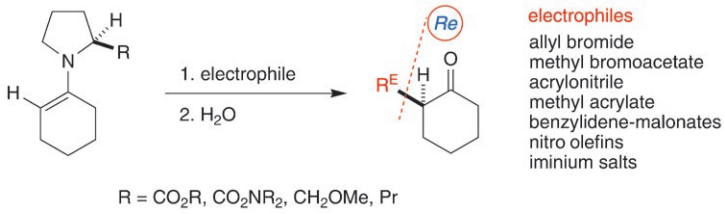
[51]) While aldehydes may have to be activated for addition to an enamine C=C bond, we do not need to provide such activation in the bond-forming step with a strong electrophile such as β-nitrostyrene. With nitro-olefins, we have to be aware of the following additional facts: *i*) their reaction with an enamine could pass through a primarily formed four- or six-membered ring (*cf.* **14** and **15**), which then rearranges to the observed product-oxazolidinone; *ii*) their reactions with enamines are reversible [29d]; *iii*) the colors seen when an enamine and a β-nitrostyrene are mixed – even at −75° – may be an indication that charge-transfer complexes, or even one-electron transfer processes could be involved.

[52]) The $pK_a$ of the proline $CO_2H$ group is 2.0, the isoelectric point of proline is at pH 6.4, and its $R_2NH_2^{\oplus}$ group has a $pK_a$ of 10.6; see textbooks of Organic Chemistry and Tables in [63].

[53]) For review articles covering the use of 2-(methoxymethyl)pyrrolidine ('prolinol methyl ether) in enantioselective synthesis, see [64].

[29b]. For cyclohexenyl-pyrrolidines, these results are shown in *Scheme 15*[54]). In the corresponding enamines, there is neither an acidic H-atom to guide an electrophile to the nucleophilic center, nor can a cyclic intermediate, such as the oxazolidinone, be involved. Thus, there appears to be an intrinsic preference for *Re*-additions to the pyrrolidino-enamines derived from (*S*)-proline and ketones[55])[56])[57]), no matter whether the reaction is carried out catalytically or stoichiometrically, and no matter whether H-bonding or heterocyclization is possible or not.

*Scheme 15*




8.2. *Organocatalysis with Pyrrolidines Carrying Bulky Diarylmethyl-Substituents at C(2)*. An important and consistent exception to the rule of preferred *Re*-face attack is provided by the observation in various studies employing, as organocatalysts, pyrrolidines substituted at C(2) by sterically extremely demanding substituents $(Aryl)_2CH$ or $(Aryl)_2(RO)C$, with which very high preferences of *Si*-attack to the enamine C=C bond are reported. This reversal of stereochemical preference holds for

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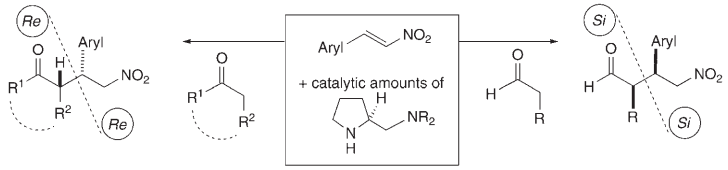
54) In judging the value of mechanistic conclusions, we have to be aware of the fact that – with the exception of the *Michael* additions of the prolinol ether-derived enamines – the enantioselectivities of the stoichiometric reactions are mostly low.

55) These include catalytic reactions of ketones involving derivatives of (*S*)-proline in which the COOH group is replaced by substituents such as carboxamide [37][65], sulphonylimide [53a][66], (sulfonylamino)methyl [39][67], aminomethyl [31][68][69], tetrazolyl, or tetrazolylmethyl [53].

56) Besides the proline-catalyzed additions of aldehydes to nitro-olefines (*Si*,*Si*-combination of the trigonal centers; *cf. Footnote 35*), there are other exceptions to the '*Re*-rule' involving aldehydes: prolinol methyl ether-catalyzed (20 mol-%) additions of aldehydes to the ethyl *N*-(4-methoxyphenyl)iminoglyoxylate take place from the *Si*-face of the assumed intermediate enamine of (*E*)-double-bond geometry [70]. Also 2-(aminomethyl)pyrrolidines and a bipyrrolidine generally catalyze the *Michael* additions of ketones to nitro-olefines with *Re/Re* and of aldehydes with *Si/Si* topicities [31][46a][68][69]:

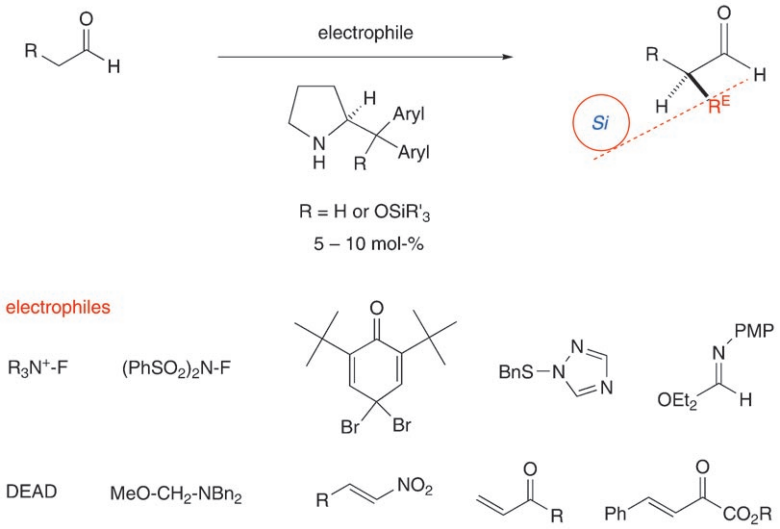



For an attempted interpretation using the steric-repulsion-controlled model (*cf.* **J**, below), see [68]; in this paper, the formation of regioisomeric products from unsymmetrical ketones and nitro-olefins is reported (*cf. Footnote 35*).

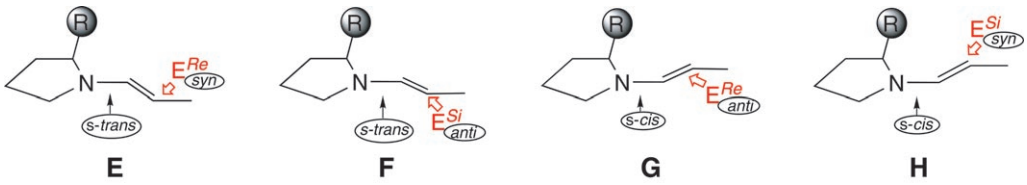
57) *Re*-Attack occurs also in the DEAD-amination of an $\alpha$-branched aldehyde (2-phenylpropanal) [71].

the large variety of reactions, listed in *Scheme 16*[58])[59]), and the consistency by which these 'obese' substituents lead to preferred *Si*-attack is comparable with the regularity, with which *Re*-attack is observed in systems bearing 'normal-size' substituents.

*Scheme 16*




**9. Mechanistic Discussion.** – In principle, there are four different stereochemical variants, **E**–**H**, by which an electrophile can add to the C=C bond of a pyrrolidino-enamine: the electrophile enters *syn* to the substituent at C(2) (on the same side of the 'plane' defined by the pyrrolidine ring) with the axis of the enamine C=C bond pointing away from the substituent $E^{Re}$(*syn*, s-*trans*) (**E**), or the electrophile enters *anti* to the substituent, again in the s-*trans*-conformation of the double bond $E^{Si}$(*anti*, s-*trans*) (**F**), while with the s-*cis*-conformation the two variants are $E^{Re}$( *anti*, s-*cis*) (**G**), and $E^{Si}$(*syn*, s-*cis*) (**H**). Both, *syn*- and *anti*-modes have been discussed in the literature to rationalize the observed stereochemical outcome of reactions. In discussions of *syn*-



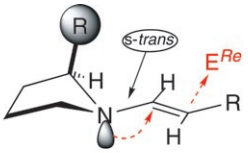

[58]) For leading references, see a recent 'highlight' article [72].

[59]) The *geminal-diaryl effect* was actually first exploited in organic synthesis with the TADDOLs, carrying two $(Aryl)_2(HO)C$ groups [73]. For a brief review article about the *geminal*-diaryl effect in enantioselective organic synthesis, see [74].

additions (mode **E** and **H**) terms such as 'polar, electrostatic, *Coulombic*' interactions, 'stabilization of zwitterions', 'intramolecular solvation', 'antisteric effects' were used [29][53a][64][70]. In discussions of *anti*-additions (modes **F** and **G**), minimalization of steric repulsion was suggested to control the course of the reaction [72].

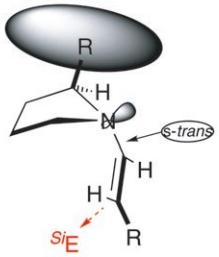
For our further mechanistic discussion, it is advisable to first consider what is known about the configurational and conformational structure of pyrrolidino-enamines. A search in the literature shows that the ETH paper of 1978 [9] is still the only source of X-ray information about the structure of pyrrolidino-enamines. While enamines derived from piperidine and morpholine [9][29a] have an extensively pyramidalized N-atom[60]), only an enamine carrying an unsubstituted pyrrolidine showed, among the systems investigated, an essentially planar enamine group [9][61]). However, the two enamines derived from six-membered-ring ketones, and a proline amide and a $\beta$-homoproline amide, respectively, were found to contain a distinctly pyramidalized N-atom in the solid state [9]. In both examples, the substituent at C(2) of the pyrrolidine ring is in *trans*-position to the virtual lone-pair lobe at the enamine N-atom and assumes a *pseudoaxial* orientation with regard to the average pyrrolidine ring plane (*cf.* **I**).

**I**



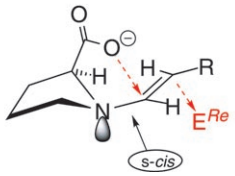

'normal'-size 2-substituent (*cf.* **E**)
quasi-*axial*-*equatorial*
*cis*-disubstituted pyrrolidine ring
lone-pair assisted E approach
H-bond activation of E possible (R = $CO_2H$)

**J**




'obese' 2-substituent (*cf.* **F**)
quasi-*diaxial*
*trans*-disubstituted pyrrolidine ring
steric-repulsion-controlled
lone-pair assisted E approach

**K**




carboxylate anion as 2-substituent (*cf.* **G**)
quasi-*axial*-*equatorial*
*cis*-disubstituted pyrrolidine ring
carboxylate assistance overrides
lone-pair assistance

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60) For further examples, including piperazine-derived enamines, see the *Cambridge*-file structures encoded as CANPEM, CETZUW, CMSMOC, COVWIT, VUTKEA, XAGYAF, YORKEV, ZIBZAL, TMVPIP (six-membered-ring amine components) and CETZUW (a 'double' enamine, from pyrrolidine and a cyclooctanedione derivative, with pyramidalized N-atoms).

61) See Fig. 2, p. 3111, in [9].

It is likely that such a *trans*-arrangement of substituent and virtual lone-pair lobe cannot simply be extrapolated for the structures of enamines that carry an unusually large substituent (*cf. Scheme 16*) at C(2), because now steric repulsion should favour a *quasi-trans*-diaxial orientation of the 'obese' group and the vinylic substituent at the N-atom, and thus make the virtual lone-pair lobe pointing into a direction that is formally *cis* to the substituent (*cf.* **J**). It is probably also safe to assume that the enamines formed from aldehydes[62]) and 'obesely' substituted pyrrolidines have s-*trans*-conformation for steric reasons, as shown in the presentation **J**. If any pyrrolidine enamine reacts under dominant steric control, then it will be one with such a large group at C(2), the electrophile approaching the enamine C=C bond in s-*trans*-conformation from the direction *anti* to the substituent. This, of course, is the interpretation that is consistently given in the literature [72]. Incidentally, it corresponds at the same time to what is assumed to be also the stereoelectronically favored path (*vide infra*), provided the conformational reasoning given above with regard to the configuration at the pyramidalized N-atom in such a system is correct.

If, as there is little doubt, the *Si*-preference shown by pyrrolidino-enamines with very large substituents is the result of steric control, then the *Re*-preference of systems with substituents of lesser size must result from a dominating influence of another factor. A *Re*-attack of the electrophile on the enamine C=C bond in the s-*trans*-conformation with a *quasi*-axial lone-pair lobe, formally *trans* to the substituent (*cf.* **E** and **I**), corresponds to what one would expect if the decisive control factor were stereoelectronic in nature. Qualitative reasoning [9][29b] would predict that, in the absence of interference by any other factor, an electrophile would prefer to attack the enamine C=C-bond face that is *anti* to the virtual lone-pair lobe of the pyramidalized enamine N-atom (*cf.* **IV** in *Sect. 1*, and *Scheme 17,a*). Such reasoning is supported by considering an enamine alkylation as an extreme version of an electrophilic allylic $S_{E'}$ substitution, a reaction type experimentally known to prefer a stereochemical course that is to be interpreted as the electrophile attacking the C=C bond of the allylic system *anti* to the electron-donating leaving group (*Scheme 17,b*) [75][76][63]).

Note that the most common electrophilic additions from the diastereotopic *Re*-faces (*cf.* **I**) correspond to the stereochemical course observed for most chiral pyrrolidino derivatives. Importantly, it is also compatible with the commonly accepted mechanistic model for proline catalysis, in which the free COOH group is invoked to activate the electrophile by intermolecular H-bonding. On the other hand, the reaction mode **K**, which corresponds to our proposal of product-determining nucleophilic participation of the carboxylate group in the electrophilic addition step, does not correspond to stereoelectronically optimal lone-pair assistance. The two reaction modes **I** and **K**, both involving *Re*-attack, differ in what provides the nucleophilic assistance in the electrophilically induced addition step: the **I**-mode being lone-pair lobe assisted, the **K**-mode carboxylate-assisted.

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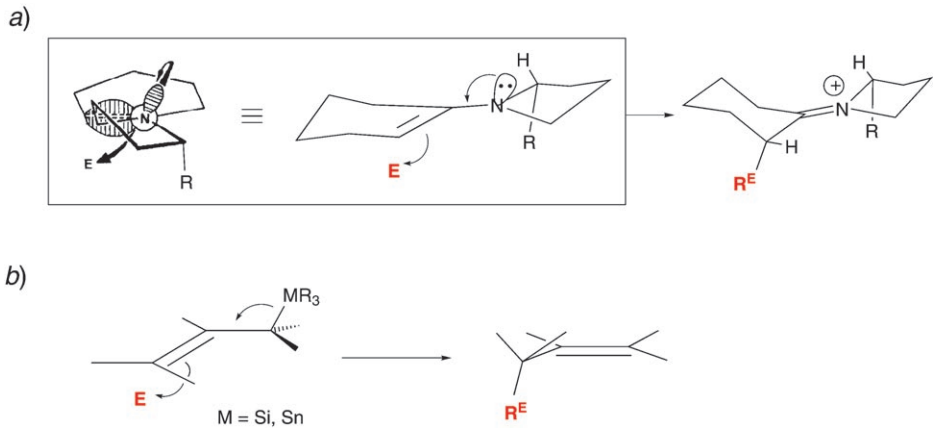
62) No reactions that would require formation of intermediate enamines from ketones and the 'obesely' substituted pyrrolidines (*cf. Scheme 16*) appear to have been reported [72].

63) See also the series of ten contributions '*Stereocontrol in organic synthesis using silicon-containing compounds*' by *I. Fleming et al.* in [76b].

Scheme 17. *Comparison of a Lone-Pair-Lobe-Assisted Addition of an Electrophile to an Enamine with an* $S_{E'}$ *Reaction. a*) In a 1983 paper by one of our groups [29b], the 'anti-steric' lone-pair-assisted addition of $\beta$-nitrostyrene to a pyrrolidino enamine was depicted as shown on the left-hand side, using the $\tau$-bond model[5]) [75][77][78]; this picture corresponds to the mode **E** and to the presentation **I**. *b*) An electrophilic allylic $S_{E'}$ substitution with *anti*-disposition of electrophile and electropositive leaving group [75][76].




Thus, we have discussed four different models:

*i*) H-bond-controlled *syn*-addition on the s-*trans*-conformation (R = COOH)
*ii*) carboxylate-assistance-controlled *anti*-addition to the s-*cis*-conformation with heterocyclization ($R = COO^-$)
*iii*) *lone-pair*-configuration-controlled *syn*-addition to the s-*trans*-conformation
*iv*) steric-repulsion-controlled anti-addition to the s-*trans*-conformation with 'obese' substituents at C(2) of the pyrrolidine

Considering the large variety of substituents on the pyrrolidine ring, which have been tested so far, and the multitude of conditions, which have been employed to carry out the reactions, there is no doubt that in referring to '*the*' mechanism of stereoselection in reactions mediated by proline and its derivatives leading to a given stereochemical outcome, such as *Re*-addition, is inadequate. There must exist a landscape of finely-tuned and interconnected mechanistic pathways that are dependent on the plethora of parameters that have been varied[64])[65])[66]) in experimental studies, and, not least, on whether the reactions are run under homogeneous or heterogeneous conditions [62d][80].

*M. L.* gratefully acknowledges fellowships from the *German Merit Foundation* (*Studienstiftung des Deutschen Volkes*) during undergraduate (2000–2002) and graduate studies (2002–2004). We gratefully

64) Structure of the R group at C(2) of the pyrrolidine, reactant ratio, temperature, solvent properties, presence of $H_2O$ and of additives such as acids, bases, Li-salts, molecular sieves, *etc.*
65) For very special reaction conditions (solvent-free in a ball mill), see [79].
66) See also the reversal of topicities in the (aminomethyl)pyrrolidine-catalyzed *Michael* additions to nitro-olefines when going from aldehydes to ketones, as outlined in *Footnote 56*.

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*Pro memoria: D. S.* gedenkt seiner verstorbenen Frau *Inge Seebach*, in Dankbarkeit für das grosszügige Verständnis und die Geduld, welche sie dem Forscher und Autor über ein halbes Jahrhundert des Zusammenseins angedeihen liess, auch beim Schreiben des Manuskriptes der vorliegenden Veröffentlichung, welches sich über einen Zeitraum von mehr als einem Jahr hingezogen hat.

## Experimental Part

1. *General*. Solvents for chromatography and workup procedures were distilled from *Sikkon* (anh. $CaSO_4$; *Fluka*) and from KOH ($Et_2O$). $CHCl_3$ and $CCl_4$ were filtered over basic $Al_2O_3$ (Alumina, *Woelm N*, activity I). $Et_3N$ and DIPEA were distilled from $CaH_2$ and stored over KOH. Ultra high vacuum ($1.9 \cdot 10^{-5}$ mbar) was obtained using a *Balzers 022-065D* Turbomolecular pump. Abbreviations: DIPEA: $EtN(i\text{-}Pr)_2$, HFIP: 'hexafluoroisopropanol' ($=(CF_3)_2CHOH$), h.v.: high vacuum (0.01 – 0.1 mbar), TFA: $CF_3COOH$. TLC: *Merck* silica gel *60 $F_{254}$* plates; detection under UV light at 254 nm and monitoring by solutions of 'Mo-stain' (25 g of phosphomolybdic acid, 10 g of $Ce(SO_4)_2 \cdot H_2O$, 60 ml of conc. $H_2SO_4$, 940 ml of $H_2O$), followed by heating with a heat gun. FC: *Fluka* silica gel *60* (40 – 63 mesh); the dimensions of the columns are given as 'diameter × height of the silica column'. M.p.: in open-end glass capillary tubes on a *Büchi 510* apparatus; uncorrected. Optical rotations $[\alpha]_D$: *Perkin-Elmer 241* polarimeter (10 cm, 1 ml cell). The solvents, temp., and concentrations (*c* in g/100 ml) are indicated. IR Spectra: measured as 1 – 3% $CHCl_3$ soln. when not stated otherwise on a *Perkin-Elmer 257* spectrophotometer, or neat on a *Perkin-Elmer 1600 FT-IR* spectrophotometer. NMR Spectra: $^1$H-NMR spectra were recorded on a *Varian Gemini-300* (300 MHz) or *HA-100 D* (100 MHz), *Perkin Elmer R-24 A* (60 MHz). $^{13}$C-NMR Spectra were recorded on a *Bruker AMX-400* (100 MHz) or *Varian Gemini-300* (75 MHz). Chemical shifts $\delta$ are given in ppm relative to resonances of solvent ($^1$H: 7.26 ppm for $CDCl_3$, 1.73 ppm for ($D_8$)THF, 7.16 ppm for $C_6D_6$, 11.65 ppm for $CD_3COOD$, 11.50 ppm for (D)TFA, 4.40 ppm for ($D_2$)HFIP; $^{13}$C: 77.0 ppm for $CDCl_3$, 25.4 ppm for ($D_8$)THF, 128.4 ppm for $C_6D_6$, 20.0 ppm for $CD_3COOD$, 116.6 ppm for (D)TFA, 123.6 ppm for ($D_2$)HFIP), or TMS as internal standard; coupling constants *J* are given in Hz. The multiplicities of signals were determined by the DEPT technique: DEPT: + = primary or tertiary (positive DEPT signal), − = secondary (negative DEPT signal), $C_q$ = quaternary C-atoms. MS: *Hitachi RMU-6A* and *RMU-6D* (the approximate temp. is given in each case. Abbreviations: Td (direct supply), Ti (indirect supply)), *VG Tribrid* (EI), *Bruker Reflex* (MALDI), or *IonSpec Ultima 4.7 T FT* ion cyclotron resonance (ICR, HR-MALDI, in a 2,5-dihydroxybenzoic acid matrix) mass spectrometer in *m/z* (% of basis peak). GC: *Fractovap 2200* with He as carrier gas (45 ml/min). Stationary phase and column temp. are given. Chiral HPLC: *Waters 515* HPLC *pump*, *Waters 484* tuneable absorbance detector, *Waters* automated gradient controller; column: *Chiralpak AD-H* (0.46 × 25 cm). Flow 1 ml/min.

1.1. *FT-IR-Apparatus (ReactIR): Mettler Toledo* reaction analysis system *ReactIR4000*, *MCT* mid-band Detector 24 h, probe ZnSe, diameter 16.0 mm, resolution 4 $cm^{-1}$; *Dell* GX270/2.8 GHz, 1 GB RAM, 40 GB HD, WIN-XP; *ReactIR* software version 3.0. Reaction vessel: 10 ml three-necked flask equipped with magnetic stirring, septum inlet, Ar flushing, and a special neck for the IR probe. The IR-sensitive tip of the IR probe was placed directly above the magnetic stirrer.

2. *Synthesis of the Compounds. 1-(Cyclohex-1-enyl)pyrrolidine. Variant A.* Mol. sieves (4 Å; *ca.* 2 g, activated at 200° in the h.v. for 2 h) were placed in a *Dean – Stark* water separator, which was attached to a round-bottom flask containing a magnetic stirrer bar. L-Proline (1.26 g, 11.0 mmol) was added, followed by toluene (15 ml, dried by refluxing over Na). Cyclohexanone (1.00 ml, 9.65 mmol) was added, and the whole immersed in a preheated oil bath at 130° with stirring under a static atmosphere of $N_2$. After 1 h, the initially heterogeneous mixture had become completely homogeneous and had assumed a light yellow color. The mixture was checked by GC (column *S.E. 30*, flow 1 ml/min, oven 200°, injector 210°,

amplitude 256 × 1000, sample size 2 µl, retention time: cyclohexanone *ca.* 2 min, pyrrolidine enamine of cyclohexanone: 6 min) by comparison to a simulated soln. of the pyrrolidine enamine of cyclohexanone in toluene corresponding to 100% reaction. The area of the actual and simulated peaks was identical (± 5% average of triplicate injections). The solvent was removed by distillation at atmospheric pressure. The residual oil was distilled in a *Kugelrohr* oven (100°/13 mbar) to afford 767 mg (52%) of 1-(cyclohex-1-enyl)pyrrolidine.

*Variant B.* L-Proline (20.0 g, 174 mmol), cyclohexanone (200 ml, 1.93 mol), TsOH (2.00 g, 11.6 mmol), and benzene (200 ml) were added to a round-bottom flask containing a stirrer to which a *Dean–Stark* water separator was attached. The suspension was refluxed for 12 h. The resulting yellow soln. was cooled to r.t., filtered over a pad (5 × 5 cm) of basic $Al_2O_3$ (Alumina, *Woelm N*, activity I), volatiles were removed under vacuum, and the residue was distilled (b.p. 111°/14 mbar ([48]: 105–107°/13 mm Hg; [81]: 108–109°/20 mm Hg)) to give 21.1 g (80%) of 1-(cyclohex-1-enyl)pyrrolidine as a colorless liquid. IR ($CCl_4$): 3040*w*, 2960*s*, 2920*s*, 2910*s*, 2540*w*, 2430*w*, 1710*s*, 1635*s*, 1455*m*, 1445*m*, 1430*m*, 1390*m*, 1350*w*, 1345*m*, 1335*w*, 1300*m*, 1260*m*, 1240*w*, 1220*w*, 1180*m*, 1150*m*, 1140*w*, 1115*w*, 990*m*, 910*m*. $^1$H-NMR (300 MHz, $C_6D_6$): 1.15–2.26 (*m*, 12 H); 2.85–2.89 (*m*, 4 H); 4.41 (br. *t*, *J* = 3.8, CH). $^{13}$C-NMR (75 MHz, $C_6D_6$, DEPT): 23.8 (–, $CH_2$); 24.0 (–, $CH_2$); 25.0 (–, $CH_2$); 25.2 (–, $CH_2$); 27.1 (–, $CH_2$); 28.0 (–, $CH_2$); 41.9 (–, $CH_2$); 47.6 (–, $CH_2$); 93.5 (+, CH); 143.1 ($C_q$). MS (*RMU-6A*, Ti 200°): 152 (12), 151 (100), 150 (100), 137 (7), 136 (65), 124 (10), 123 (92), 122 (55), 110 (17), 109 (5), 108 (33), 98 (23), 97 (6), 96 (15), 95 (60), 94 (30), 93 (6), 91 (5), 83 (7), 82 (7), 81 (18), 80 (23), 79 (14), 77 (11), 71 (9), 70 (42), 69 (20), 68 (13), 67 (16), 66 (5), 65 (5), 56 (11), 55 (68), 54 (33), 53 (22), 52 (6), 51 (9), 43 (37), 42 (63), 41 (67), 40 (11), 39 (43), 38 (5), 30 (6), 29 (16), 28 (28), 27 (38), 26 (6), 18 (9). Anal. data in accordance with those in [81].

*(*S*)-1-(Trimethylsilyl)proline Trimethylsilyl Ester.* According to a literature procedure [19], a vigorously stirred suspension of L-proline (3.50 g, 30.0 mmol) in diethyl(trimethylsilyl)amine (13.3 ml, 70.0 mmol) was heated to 110° in a distillation apparatus (dried by heat gun at 1.2 mbar) for 2 h under $N_2$. As the reaction progressed, $Et_2NH$ was distilled from the mixture, which became homogeneous. After 2 h, the resulting soln. was allowed to cool to r.t. and the (*S*)-proline ester was obtained by distillation (58–56°/1.6 mbar, ([82]: 76°/4 mbar; [15]: 56°/0.13 mbar)) as a colorless liquid (4.92 g, 63%). $^1$H-NMR (300 MHz, $CDCl_3$): 0.04 (*s*, $Me_3SiN$); 0.25 (*s*, $Me_3SiO$); 1.62–2.06 (*m*, 2 $CH_2$); 2.98–3.11 (*m*, $CH_2N$); 3.82 (*dd*, *J* = 8.4, 3.2, $CHCO_2$). $^{13}$C-NMR (75 MHz, $CDCl_3$): –0.87; –0.32; 25.8; 31.7; 47.0; 61.6; 177.5. Spectral properties in accordance with those in [15][82].

*(2*R,5S*)-3-(*tert*-Butyl)-3-oxo-1-azabicyclo[3.3.0]octan-4-one* (**2a**). Pivalaldehyde (110 µl, 87.9 mg, 1.02 mmol), $CCl_4$ (250 µl, 411.6 mg), and (*S*)-1-(trimethylsilyl)proline trimethylsilyl ester (280 µl, 256.5 mg, 0.99 mmol) (in that order) were added to a dry NMR tube. The soln. was shaken in order to ensure complete mixing and then placed in an oil bath at 40°. Care was taken after the addition of the proline derivative to keep the tube sealed from the atmosphere at all times. After 2 h, $^1$H-NMR analysis revealed that the desired product was the only observed species. The contents of the NMR tube could be distilled (all transfers *etc.* in a dry box) in a *Kugelrohr* oven (65°/h.v.) to afford 145.6 mg (80%) of **2a**. IR ($CCl_4$): 2960, 2920, 2875, 1775*s*, 1480, 1460, 1450, 1395, 1360, 1340 (sh), 1330, 1320 (sh), 1295, 1275, 1240, 1215 (sh), 1185*s*, 1165 (sh), 1119, 1092, 1075, 1030, 990 (sh), 972, 965 (sh), 900, 890*w*. $^1$H-NMR (100 MHz, $CDCl_3$): 0.95 (*s*, $^t$Bu); 1.77 (*m*, $CH_2$(7)); 2.08 (*m*, $CH_2$(6)); 3.00 (*m*, $CH_2$(8)); 3.82 (*dd*, CH(5)); 4.52 (*s*, CH(2)). MS (*RMU-6D*, Ti 200°): 139 (17), 124 (8), 109 (5), 83 (8), 82 (100), 81 (5), 80 (5), 71 (5), 70 (7), 69 (5), 68 (10), 67 (5), 55 (14), 53 (5), 44 (40), 43 (10), 42 (8), 41 (15), 39 (8), 29 (8), 28 (10), 27 (7). Anal. data in accordance with those in [16]. For a more convenient *Org. Synth.* procedure with acid catalysis, see [16c].

*4-(*tert*-Butyl)-3a,4,6,7,8,8a-hexahydro-2-phenylpyrrolo[3,4-*a*]pyrrolizine-1,3-dione* (**7**). A dry round-bottom flask (25 ml) with a reflux condenser (0° cooling water) and a magnetic stirrer was charged with toluene (10 ml), L-proline (1.18 g, 10.3 mmol), 4-Å mol. sieves (2.0 g, freshly activated), pivalaldehyde (1.1 ml, 10.0 mmol), and *N*-phenylmaleinimide (2.0 g, 11.56 mmol). The whole flask was immersed in a preheated oil bath at 125° and maintained under reflux for 4.6 h. At the end of this time, the flask was removed from the bath and allowed to cool to r.t. to give a reddish mother liquor above a light tan precipitate. The material was transferred off the mol. sieves and washed with toluene (3 × 2 ml). Removal of the solvent under h.v. at r.t. yielded 3.40 g of **7** (99.5%). Light pinkish foam. This solid

consisted of four major compounds as indicated by TLC ($SiO_2$, $CH_2Cl_2$/AcOEt 9:1, $R_f$ 0.16, 0.37, 0.51, 0.65) plus some minor ones. Repeated chromatography (five columns, fraction containing the diastereoisomers were combined) using the same solvent combination or closely similar ones resulted in the isolation of the two less polar diastereoisomers: diastereoisomer *a* (1.24 g, $R_f$ 0.37) and diastereoisomer *b* (368 mg, $R_f$ 0.16). Total yield: 52%.

*Diastereoisomer* a: M.p. 90–91.5°. IR ($CHCl_3$): 3020*w*, 2960, 2940 (sh), 2910, 2870, 1775*w*, 1710*s*, 1600*w*, 1500*s*, 1478*w*, 1465*w*, 1458*w*, 1380*s*, 1360, 1355 (sh), 1230–1200 (br.), 1185, 1172, 1120*w*, 915*w*, 825*w*, 690, 615*w*. $^1$H-NMR (100 MHz, $CCl_4$): 0.96 (*s*, 9 H); 1.17 (*m*, 4 H); 1.84 (*m*, 4 H); 2.60 (*m*, 1 H); 3.86 (*m*, 1 H); 7.25 (*m*, 5 H). $^{13}$C-NMR (25 MHz, $CDCl_3$): 26.2 (*t*, 1 C); 26.8 (*q*, 3 C); 28.0 (*t*, 1 C); 36.4 (*s*, 1 C); 50.0 (*d*, 1 C); 50.8 (*d*, 1 C); 58.4 (*t*, 1 C); 68.4 (*d*, 1 C); 80.4 (*d*, 1 C); 127.2 (*d*, 2 C); 129.6 (*d*, 1 C); 130.4 (*d*, 2 C); 133.4 (*s*, 1 C); 178.4 (*s*, 1 C); 180.6 (*s*, 1 C). MS (*RMU-6A*, Td < 75°): 312 (2), 297 (5), 256 (28), 255 (100), 163 (3), 149 (4), 109 (4), 108 (32), 80 (10), 57 (4), 53 (4), 41 (7), 31 (4), 29 (4), 18 (8). Anal. calc. for $C_{19}H_{24}N_2O_2$ (312.4): C 73.04, H 7.74, N 8.97; found: C 73.08, H 7.75, N 8.96.

*Diastereoisomer* b: $^1$H-NMR (100 MHz, $CDCl_3$): 1.11 (*s*, 9 H); 1.84 (*m*, 3 H); 2.16 (*m*, 1 H); 2.70 (*m*, 1 H); 3.14 (*m*, 3 H); 3.73 (*m*, 2 H); 7.32 (*m*, 5 H). $^{13}$C-NMR (25 MHz, $CDCl_3$): 25.6 (*t*, 1 C); 28.0 (*q*, 3 C); 32.2 (*t*, 1 C); 36.2 (*s*, 1 C); 50.0 (*d*, 1 C); 53.0 (*d*, 1 C); 57.8 (*t*, 1 C); 69.0 (*d*, 1 C); 80.6 (*d*, 1 C); 127.2 (*d*, 2 C); 129.6 (*d*, 1 C); 130.4 (*d*, 2 C); 133.6 (*s*, 1 C); 178.0 (*s*, 2 C). MS (*RMU-6D*, Td < 80°): 297 (4), 256 (17), 255 (100), 149 (10), 125 (4), 124 (4), 123 (3), 111 (6), 109 (7), 108 (35), 97 (10), 96 (5), 95 (9), 93 (4), 91 (4), 85 (9), 83 (11), 82 (5), 81 (12), 80 (11), 79 (5), 77 (5), 71 (14), 70 (6), 69 (15), 68 (4), 67 (9), 57 (20), 56 (5), 55 (15), 53 (4), 43 (13), 41 (15), 29 (7), 18 (6).

*(5′S)-Spiro[cyclohexane-1,2′-3-oxa-1-azabicyclo[3.3.0]octan]-4′-one* (**8**). *Variant A.* A dry NMR tube was charged with cyclohexanone (118 mg, 1.20 mmol), $CCl_4$ (704.1 mg), and (*S*)-1-(trimethylsilyl)proline trimethylsilyl ester (280.1 mg, 1.08 mmol) in that order. The soln. was shaken to ensure complete mixing. A spontaneous reaction occurred within 15 min at r.t. to afford a milky white opaque soln. The material was transferred to a flame-dried 10-ml round-bottom flask in the dry box. After removal of the solvent (h.v., r.t.) the resulting orange-yellow material was distilled in a *Kugelrohr* oven (95°/h.v.) in a rigorously $H_2O$-free system. The distilled compound **8** was dissolved in $CCl_4$ in the dry box (the soln. was pale, presumably due to hydrolysis with proline formation)[67]). IR ($CCl_4$): 2940, 2860, 1772, 1714*w*, 1450, 1380, 1370, 1337, 1310, 1265, 1210, 1147, 1130, 1080, 1065, 950, 920, 890, 879. For part of the IR spectrum of **8** in THF, see *Fig. 2*.

*Variant B.* (*S*)-1-(Trimethylsilyl)proline trimethylsilyl ester (4.92 g, 19.0 mmol) was dissolved in dry $CH_2Cl_2$ (40 ml) under Ar in a two-necked flask (dried by heat gun at 1.2 mbar) containing a stirrer bar, fitted with a stopper and a gas inlet. The soln. was cooled to −20°, and cyclohexanone (1.97 ml, 19.0 mmol), followed by piperidine (188 µl, 1.90 mmol), was added dropwise[68]). The stirred mixture was allowed to warm to r.t., and stirring was continued overnight (18 h). After 30 min, the mixture became turbid, and after 18 h a thick suspension formed. This was first concentrated under vacuum (60 mbar, followed by 1.2 mbar) and then submitted to *Kugelrohr* distillation with a turbo-molecular pump (76–78°/$1.9 \cdot 10^{-5}$ mbar) to give the desired product **8** as a colorless oil (2.20 g, 59%), which could be stored at −20° for several weeks in a *Schlenk* tube, but discolored rapidly on standing at r.t. $[\alpha]_D^{r.t.} = -18.6$ (*c* = 1.60, $CHCl_3$). IR (THF): 2972, 2937, 2856, 1772, 1459, 1208, 1061, 899. $^1$H-NMR (300 MHz, $CDCl_3$): 1.33–2.02 (*m*, 6 $CH_2$); 2.11–2.22 (*m*, $CH_2$); 2.66 (*ddd*, *J* = 10.4, 9.2, 5.8, 1 H, $CH_2N$); 2.90–2.95 (br. *m*, 1 H, $CH_2N$); 4.05 (*dd*, *J* = 9.7, 4.3, $CHCO_2$). $^{13}$C-NMR (75 MHz, $CDCl_3$): 23.0; 23.1; 24.8; 25.4; 26.5; 31.9; 37.3; 47.4; 63.1; 105.4 (CON); 177.9 (*s*). EI-MS: 231 (30), 230 (10), 195 (37), 188 (11), 177 (26), 167 (28), 162 (13), 151 (71), 150 (41), 136 (20), 124 (20), 123 (38), 122 (18), 108 (12), 98 (15), 80 (17), 70 (100), 69 (10), 68 (13), 67 (10), 55 (50), 54 (14), 53 (11), 43 (11), 42 (39), 41 (49), 39 (22), 28 (14), 27 (21). HR-EI-MS: 195.1264 ($C_{11}H_{17}NO_2^+$; calc. 195.1259).

u-*2-(2-Nitro-1-phenylethyl)cyclohexanone* (**9**). a) *Reaction without DBU at r.t.* Oxazolidinone **8** (330 mg, 1.69 mmol) was dissolved in dry THF (8 ml) under Ar in a *Schlenk* flask (dried by heat gun at

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67) Interestingly, when analytically pure (*S*)-1-(trimethylsilyl)proline trimethylsilyl ester was used in dry $CH_2Cl_2$, no reaction occured.

68) When (*S*)-1-(trimethylsilyl)proline trimethylsilyl ester containing small amounts (≤10%) of non-silylated proline was used, the reaction occured without adding any base.

1.2 mbar), containing a stirrer bar and fitted with a stopper. The mixture was cooled to 0°, (*E*)-*β*-nitrostyrene (265 mg, 1.77 mmol) was added, and the mixture was allowed to warm to r.t., stirred at r.t. for 48 h, then the reaction was quenched with $H_2O$ (1 ml). The mixture was diluted with $H_2O$ (10 ml) and extracted with AcOEt (3 × 10 ml). The org. layers were combined and dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by FC (2 × 25 cm; 20% AcOEt/pentane) to give **9** as a white solid (234 mg, 56%, 94% ds, 60:40 er).

b) *Reaction with DBU at Low Temp.* Oxazolidinone **8** (1.12 g, 5.75 mmol) was dissolved in dry THF (20 ml) under Ar in a two-necked flask (dried by heat gun at 1.2 mbar), containing a stirrer bar, and fitted with a stopper and a gas inlet. The mixture was cooled to −78°, and DBU (86 µl, 0.57 mmol) was added, followed by (*E*)-*β*-nitrostyrene (900 mg, 6.03 mmol). The mixture was stirred at −78° for 6 h, then the reaction was quenched with $H_2O$ (5 ml), and the mixture was warmed to r.t. The mixture was diluted with both $H_2O$ (50 ml) and AcOEt (50 ml). The resulting emulsion was left to stand, and, when two layers formed, they were separated. The org. layer was dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by FC (2 × 25 cm; 20% AcOEt/pentane) to give **9** (500 mg, 35%, 97% ds, 60:40 er). White solid. HPLC (*Chiralpak AD-H*, 0.46 × 25 cm, hexane/i-PrOH: 95:5, 1 m/min, 230 nm): 14.60 min (1*R*,2*S*)-**9**, 18.54 min (2*S*,1*R*)-**9**. Abs. configuration [29][38] was determined by comparison of HPLC data with the data obtained from repeating a literature experiment [27b], and with the racemate. $^1$H-NMR (300 MHz, $CDCl_3$): 1.10–1.24 (*m*, 1 H, $CH_2$); 1.43–1.75 (*m*, 2 $CH_2$); 1.98–2.06 (*m*, 1 H, $CH_2$); 2.31 (*tdd*, *J* = 12.4, 5.8, 1.0, 1 H, $CH_2$); 2.41 (*dddd*, *J* = 12.4, 4.9, 3.7, 1.5, 1 H, $CH_2$); 2.62 (*dddd*, *J* = 11.8, 9.9, 4.8, 0.8, CHC=O); 3.69 (*td*, *J* = 9.9, 4.8, PhC*H*); 4.56 (*dd*, *J* = 12.5, 9.9, 1 H, $CH_2NO_2$); 4.87 (*dd*, *J* = 12.5, 4.8, 1 H, $CH_2NO_2$); 7.22 (*m*, 2 arom. H); 7.10 (*m*, 3 arom. H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 25.0; 28.5; 33.2; 42.6; 43.8; 52.3; 78.8; 127.4; 127.9; 128.6; 137.5; 211.6. Spectroscopic data in accordance with those in [38][83].

c) *Reaction with DIPEA at Low Temp.* Oxazolidinone **8** (241 mg, 1.22 mmol) was dissolved in dry THF (5 ml) under Ar in a *Schlenk* flask (dried by heat gun at 1.2 mbar), containing a stirrer bar and fitted with a stopper. The mixture was cooled to −78°, and DIPEA (21 µl, 0.12 mmol) was added, followed by (*E*)-*β*-nitrostyrene (183 mg, 1.22 mmol). The mixture was stirred at −78°, and aliquots were removed as the reaction progressed. Each aliquot (0.3 ml) was removed with a pre-cooled syringe, the reaction was immediately quenched in $H_2O$ (1 ml), and the mixture was extracted with AcOEt (2 ml). The org. extract was dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was analyzed by $^1$H-NMR.

u- *and* l-*2-(2,2,2-Trichloro-1-hydroxyethyl)cyclohexanone* (*u*/*l*-**10**). a) *Reaction without DBU at r.t.* Oxazolidinone **8** (439 g, 2.25 mmol) was dissolved in dry THF (10 ml) under Ar in a two necked flask (dried by heat gun at 1.2 mbar), containing a stirrer bar, and fitted with a stopper and a gas inlet. The mixture was cooled to 0°, and chloral (0.35 ml, 2.4 mmol) was added by syringe. The mixture was warmed to r.t., stirred at r.t. for 48 h, and then the reaction was quenched with $H_2O$ (1 ml). The mixture was diluted with both $H_2O$ (10 ml) and AcOEt (10 ml). The layers were separated, and the org. layer was washed with more $H_2O$ (2 × 10 ml). The org. layers were combined, dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by FC (2 × 25 cm; 20% $Et_2O$/hexane) to give **10** (385 mg, 70%, *l*/*u* 50:50, er: *l*-**10**: 70:30, *u*-**10**: 52:48). White solid. HPLC (*Chiralpak AD-H*, 0.46 × 25 cm, hexane/i-PrOH 50:1, 1 ml/min, 210 nm): 19.23, 25.63, 29.85, 35.82, 43.04 min ([36b]: 16.02 min (*u*-**10**), 20.56 min (*u*-**10**), 26.48 min (*l*-**10**, major), 32.75 (*l*-**10**, minor)). Determination of abs. configuration by HPLC and comparison of the anal. data was accomplished as described in [36].

b) *Reaction with DBU at Low Temperature.* Oxazolidinone **8** (1.13 g, 5.77 mmol) was dissolved in dry THF (20 ml) under Ar in a two-necked flask (dried by heat gun at 1.2 mbar), containing a stirrer bar, and fitted with a stopper and a gas inlet. The mixture was cooled to −78°, and DBU (86 µl, 0.57 mmol) was added by syringe, followed by chloral (0.59 ml, 6.1 mmol). The mixture was stirred at −75° for 18 h, then the reaction was quenched with $H_2O$ (5 ml), and the mixture was warmed to r.t. The mixture was diluted with both $H_2O$ (50 ml) and AcOEt (50 ml). The layers were separated, and the org. layer was washed with $H_2O$ (2 × 50 ml). The org. layers were combined, dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by FC (2 × 25 cm; 20% $Et_2O$/hexane) to give **10**. White solid (631 mg, 45%, *l*/*u* 62:38, er: *l*-**10**: 76:24, *u*-**10**: 80:20).

$^1$H-NMR (300 MHz, $CDCl_3$): *l*-**10**: 1.59–2.56 (*m*, 8 H); 3.03 (*d*, *J* = 5.4); 3.02–3.08 (*m*, 1 H, CHOH); 5.01 (*dd*, *J* = 5.4, 2.4, CHO). *u*-**10**: 1.59–2.56 (*m*, 8 H); 3.04–3.13 (*m*, 1 H); 4.00 (*dd*, *J* = 9.8, 1.2, CHO); 6.53 (*d*, *J* = 9.8, OH).

*Observation of 2-(2-Nitro-1-phenylethyl)spiro[cyclohexane-1,2′-3-oxa-1-azabicyclo[3.3.0]octan]-4′-one* (**16**) *by* $^1$*H-NMR*. Oxazolidinone **8** (72 mg, 0.37 mmol) was dissolved in anh. ($D_8$)THF (0.4 ml) under Ar in a NMR tube with a *Young*'s tap (dried by heat gun at 1.2 mbar). (*E*)-*β*-Nitrostyrene (55 mg, 0.37 mmol) was added, the NMR tube was shaken, and, within 10 min, NMR measurements were initiated. Measurements were complete within 5 h. $^1$H-NMR (300 MHz, ($D_8$)THF; mixture of diastereoisomers (I–IV); see *Fig. 3*): 1.12–2.35 (*m*, 26 H); 2.36 (br. *d*, *J* = 11.0, 0.60 H, **16**(I)/(**16**(III) or **16**(IV))); 2.56–2.76 (*m*, 1.48 H); 2.80–2.91 (*m*, 1.66 H); 2.99 (*ddd*, *J* = 9.4, 6.0, 3.6, 0.35 H, **16**(II)); 3.08–3.53 (*m*, 0.34 H); 3.61–3.76 (*m*, 0.17 H); 3.83 (*m*, 0.89 H, **16**(I)/**16**(II), PhC*H*); 4.02 (*dd*, *J* = 9.7, 4.1, 0.65 H, **8**, $CHCO_2$); 4.18 (*dd*, *J* = 9.5, 4.7, 0.4 H, **16**(II)/(**16**(III) or **16**(IV)), $CHCO_2$); 4.25 (*dd*, *J* = 9.7, 4.5, 0.6 H, **16**(I)/(**16**(III) or **16**(IV)), $CHCO_2$); 4.61 (*dd*, *J* = 13.8, 7.9, 0.54 H, **16**(I), 1 H, $CH_2NO_2$); 4.69 (*dd*, *J* = 12.9, 10.9, 0.40 H, **16**(II)/**16**(III), 1 H, $CH_2NO_2$); 4.74–5.19 (*m*, 0.39 H); 5.39 (*dd*, *J* = 12.9, 4.5, 0.35 H, **16**(II), 1 H, $CH_2NO_2$); 5.27 (*dd*, *J* = 12.7, 5.0, 0.05 H, **16**(III), 1 H, $CH_2NO_2$); 5.53 (*dd*, *J* = 13.8, 6.1, 0.54 H, **16**(I), 1 H, $CH_2NO_2$); 5.76 (*dd*, *J* = 13.5, 4.6, 0.06 H, **16**(IV), 1 H, $CH_2NO_2$); 7.17–7.50 (*m*, 7.7 H); 7.71 (*m*, 0.54 H, nitrostyrene arom. H); 7.90 (*d*, *J* = 13.7, 0.29 H, PhCHC*H*$NO_2$); 8.04 (*d*, *J* = 13.7, 0.29 H, PhC*H*C$HNO_2$); *cf.* the 2D spectrum in *Fig. 3*.

*Observation of* **17** *by NMR in Different Solvents*[69]). *a*) Oxazolidinone **8** (*ca.* 100 mg, 0.5 mmol) was dissolved in $CD_3OD$ (0.7 ml). Spectra were recorded within 10 min. $^1$H-NMR (300 MHz, $CD_3OD$): 1.70–1.76 (*m*, 2 H); 1.65–1.80 (*m*, 4.3 H); 2.09–2.18 (*m*, 1 H); 2.31–2.43 (*m*, 2 H); 2.40 (*td*, *J* = 6.5, 2.7); 2.66–2.88 (*m*, 0.5 H); 3.93 (*ddd*, *J* = 13.0, 9.0, 8.0, 1 H, $CH_2N$); 4.14 (*ddd*, *J* = 13.0, 7.4, 4.0, 1 H, $CH_2N$); 4.83 (*dd*, *J* = 7.3, 3.3, CHN). $^{13}$C-NMR (75 MHz, $CD_3OD$): 24.1; 24.7; 26.6; 31.2; 34.7–35.7 (br. *m*); 55.3; 70.5; 172.5 ($CO_2$); 190.7 (C=N$^+$).

*b*) Oxazolidinone **8** (*ca.* 100 mg, 0.5 mmol) was added to solid $C_6D_5OD$ (0.9 g) in an NMR tube under Ar. The mixture was heated to 50° to melt the $C_6D_5OD$, and the tube was shaken to mix the contents. Measurements were conducted after 4 h of mixing. $^1$H-NMR (300 MHz, $C_6D_5OD$, 50°): 1.04–1.73 (br. *m*, 8 H); 1.71–2.28 (br. *m*, 5.1 H); 2.88 (*dt*, *J* = 12.4, 7.8); 3.37–3.42 (*m*); 4.49 (br. *d*, *J* = 7.9, CHN). $^{13}$C-NMR (75 MHz, $C_6D_5OD$): 22.8; 24.3; 25.0; 26.9; 30.2; 33.3–34.5 (br. *m*); 54.2; 69.0; 173.1 ($CO_2$); 191.9 (C=N$^+$).

*c*) Oxazolidinone **8** (*ca.* 100 mg, 0.5 mmol) was dissolved in ($D_2$)HFIP (0.7 ml), and measurements were performed after 40 min. $^1$H-NMR (300 MHz, ($D_2$)HFIP): 1.70–2.18 (*m*, 4.9 H); 2.41–2.87 (*m*, 8.4 H); 3.78 (*dt*, *J* = 13.9, 8.4, 1 H, $CH_2N$); 4.16 (*dt*, *J* = 11.9, 5.4, 1 H, $CH_2N$); 4.73 (br. *t*, *J* = 5.7, 1 H). $^{13}$C-NMR (75 MHz, ($D_2$)HFIP): 24.5; 24.9; 27.3; 27.4; 32.0; 36.7; 37.1; 56.6; 70.9; 175.7 ($CO_2$); 195.9 (C=N$^+$).

*d*) Oxazolidinone **8** (*ca.* 100 mg, 0.5 mmol) was dissolved in $CD_3COOD$ (1 ml), and measurements were performed after 3.5 h. $^1$H-NMR (300 MHz, $CD_3COOD$): 1.44–2.18 (*m*, 12.2 H); 2.45–2.58 (*m*, 0.5 H); 3.72–3.82 (*m*, 1 H); 3.86–3.94 (*m*, 1 H); 4.87 (*dd*, *J* = 7.4, 2.9, $CHCO_2$). $^{13}$C-NMR (75 MHz, $CD_3COOD$): 23.5; 23.9; 24.6; 25.2; 26.2; 30.3; 55.1; 68.9; 172.6 ($CO_2$); 192.2 (C=N$^+$)[70]).

*e*) Oxazolidinone **8** (*ca.* 100 mg, 0.5 mmol) was dissolved in (D)TFA (0.7 ml). $^1$H-NMR (300 MHz, (D)TFA): 1.36–2.54 (*m*, 11.6 H); 3.60–3.70 (*m*, 1 H, $CH_2N$); 3.77–3.81 (*m*, 1 H, $CH_2N$); 4.86 (br. *d*, *J* = 7.4, CHN). $^{13}$C-NMR (75 MHz, (D)TFA): 25.5; 26.2; 29.2; 29.4; 32.4; 38.4; 38.9; 57.9; 69.1; 175.1 ($CO_2$); 200.1 (C=N$^+$).

*f*) LiBr (3 micro-spatulas, dried over 18 h under vacuum, 0.5 mbar, 140°) was added to ($D_8$)THF (0.4 ml) under Ar until saturation, and a strong exothermic reaction resulted. Once this had subsided, oxazolidinone **8** (*ca.* 100 mg, 0.5 mmol) was added, and precipitation immediately occurred accompanied by another strong exothermic reaction. $^1$H-NMR (300 MHz, ($D_8$)THF): 1.57–2.08 (*m*, 9 H); 2.23–2.43 (*m*, 2 H); 2.81–3.09 (*m*, 3 H); 4.08–4.27 (*m*, $CH_2N$); 4.66 (*s*, assigned to ($D_8$)THF · $Li^+$, 0.37 of residual

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[69]) In all deuterated solvents used except ($D_8$)THF and ($D_6$)DMSO, H/D exchange was observed, resulting in an underintegration in the $^1$H-NMR measurements (see *Table 4*).

[70]) There is a minor component (*ca.* 5%) present. $^1$H-NMR: 3.11–3.27 (*m*, 0.12 H); 4.09 (*dd*, *J* = 8.7, 6.3, 0.05 H, $CHCO_2$). $^{13}$C-NMR: 177.5 (*s*, $CO_2$).

solvent peak)[71]); 5.33 (*d*, *J* = 7.7, $CHCO_2$). $^{13}$C-NMR (75 MHz, ($D_8$)THF): 23.7; 25.2; 27.7; 30.7; 35.3; 35.5; 42.3; 55.5; 69.9; 173.7 ($CO_2$); 190.8 (C=$N^+$).

*g*) Oxazolidinone **8** (*ca.* 100 mg, 0.5 mmol) was dissolved in dry ($D_6$)DMSO (0.7 ml) in an NMR tube under Ar. $^1$H-NMR (300 MHz, ($D_6$)DMSO): 1.42–1.81 (*m*, 11 H); 1.91 (*dd*, *J* = 7.3, 5.0, 2 H); 2.11 (*dd*, *J* = 10.4, 9.8); 2.64 (*ddd*, *J* = 10.0, 9.3, 5.4, 1 H, $CH_2N$); 2.91–2.96 (*m*, 1 H, $CH_2N$); 4.21 (*dd*, *J* = 9.9, 3.4, CHN). $^{13}$C-NMR (75 MHz, ($D_6$)DMSO): 22.9; 24.2; 24.9; 26.0; 31.4; 36.4; 47.0; 62.5; 107.1 (br., CON); 176.9 ($CO_2$). The NMR spectra also show the presence of *ca.* 2% proline.

*General Procedure for the 'Titration' of the Oxazolidinone* **8** *with MeOH, PhOH, and HFIP in* $C_6D_6$ *Solution*. Oxazolidinone **8** (*ca.* 100 mg, 0.5 mmol) was dissolved in dry $C_6D_6$ (0.75 ml) under Ar in an NMR tube with a *Young*'s tap (dried by heat gun at 1.2 mbar). Successive portions of protic additive were introduced under Ar (MeOH and HFIP *via* microsyringe, PhOH weighed and added in solid form). After each portion was added, the tube was sealed and shaken vigorously, and $^1$H- and $^{13}$C-NMR spectra were recorded (measurements finished $<20$ min after each addition). Selected signals are shown in *Table 3*.

*(−)-2-Oxocyclohexylpropanenitrile* (**18**). To a dry NMR tube was added cyclohexanone (93.8 mg, 0.96 mmol), $CD_3CN$ (0.5 ml, 420.5 mg), and (*S*)-1-(trimethylsilyl)proline trimethylsilyl ester (244.8 mg, 0.95 mmol) in that order. The soln. was shaken to ensure mixing and then allowed to stand at r.t. for 15 h. The reaction was followed by monitoring the formation of hexamethyldisiloxane by NMR. $Et_3N$ (96.0 mg, 0.95 mmol) was added, and the mixture was allowed to stand during 3 d at r.t. No change was observable by NMR. Acrylonitrile (55 mg, 0.96 mmol) was added, and the mixture was allowed to stand for a further 24 h at r.t. By this time, the NMR spectrum no longer showed the olefinic signals of acrylonitrile. The soln. was poured into a phosphate buffer (pH 6.9) and extracted with $Et_2O$ (3 × 10 ml). The combined org. phases were dried ($MgSO_4$) and filtered, and the solvent was removed to afford a single species (146 mg of crude, quant. yield), which was identical in every aspect (except rotation) to a racemic sample of 2-cyanoethylcyclohexanone prepared *via* the pyrrolidine enamine of cyclohexanone. Distillation in a *Kugelrohr* oven (145°/10 Torr) afforded 80 mg (56%) of pure **18**. $[\alpha]^{25}$ ($\lambda$) in EtOH: +3.8 (589), +3.96 (578), +4.10 (546), +2.32 (436), −7.08 (365); ([37c]: +3.0 (589), −4.4 (500), −3.6 (450), −10.3 (400), −192 (304, trough), 0 (290), +295 (267, peak))[72]).

*Observation of Enamino-carboxylate Amidinium Salt* **19** *by NMR*. Oxazolidinone **8** (102 mg, 0.52 mmol) was dissolved in anh. ($D_8$)THF (1 ml) under Ar in a NMR tube with a *Young*'s tap (dried by heat gun at 1.2 mbar). DBU (156 µl, 104 mmol) was added, and the NMR tube was shaken, and, within 30 min, the NMR spectra were recorded. $^1$H-NMR (300 MHz, ($D_8$)THF): 1.46–2.06 (*m*, 27 H); 2.15–2.42 (*m*, 2 H), 2.68–2.64 (*m*, 4 H, DBU, $DBUH^+$); 2.95–3.06 (*m*, 1 H, $CH_2N$); 3.11–3.20 (*m*, 1 H, $CH_2N$); 3.25 (*t*, *J* = 5.7, 4 H, DBU, $DBUH^+$); 3.37 (*dd*, *J* = 14.8, 8.2, 8 H, DBU, $DBUH^+$); 3.79 (*dd*, *J* = 7.1, 2.3, $HCO_2$); 4.00 (*t*, *J* = 3.1, CH=C). $^{13}$C-NMR (75 MHz, ($D_8$)THF): 22.1; 24.6; 24.7; 24.8; 26.0; 26.3; 28.1; 28.8; 30.4; 32.2; 33.9; 41.1; 48.5; 49.3; 54.0; 63.8; 89.9 (*C*H=C); 143.4 (CH=*C*); 164.3 (DBU/$DBUH^+$: $CN_2$); 179.0 ($CO_2$).

*Enamino-carboxylate Amidinium Salt* **20**. To a dry NMR tube was added cyclohexanone (92.5 mg, 0.94 mmol), $CD_3CN$ (0.5 ml, 391.8 mg), and (*S*)-1-(trimethylsilyl)proline trimethylsilyl ester (205.9 mg, 0.79 mmol) in that order, and the tube was sealed with the rigorous exclusion of moisture. After 15 h, the reaction was judged to be complete by the disappearance of the two NMR peaks assignable to the *N*- and *O*-TMS groups and their replacement by a single peak attributable to hexamethyldisiloxane. *Heinzer*'s base (206.2 mg, 0.99 mmol) was added to the initially heterogeneous soln. Upon contact between the two liquids, a homogeneous darkish soln. was produced, which contained mainly the complex **20** and hexamethyldisiloxane. The sample was transferred to a flame-dried 25-ml round-bottom flask with washing (3 × 0.5 ml MeCN) in the dry box. Removal of the solvent afforded 271.3 mg (85%) of the crude complex **20** as a white solid. This material could be recrystallized from benzene, but it reacted with most

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[71]) This signal was also seen, when only LiBr was dissolved in ($D_8$)THF of the quality used herein.

[72]) The literature data were obtained with a sample, which was formed from the enamine of cyclohexanone and (*S*)-ethyl prolinate. Obviously the same enantiomer is formed preferentially in both reactions.

chlorinated solvents and was easily hydrolyzed by wet solvents[73]). M.p. 161–163°. IR ($CHCl_3$): 3400–3200 (br.), 2960, 2870, 1660*s*, 1530 (br.), 1460, 1390, 1380 (sh), 1375 (sh), 1340, 1300–1170 (br.), 1157*s*, 1080*w*. $^1$H-NMR (60 MHz, $CD_3CN$): 1.10, 1.15 (2*s*, 15 H); 1.26–2.40 (*m*, 20 H); 2.93 (*m*, 2 H); 3.60 (br. *t*, 1 H); 3.93 (br. *t*, 1 H); 11.30 (br. *s*, 2 H). MS (*RMU-6D*, Td 80°): 208 (15), 194 (15), 193 (100), 181 (5), 180 (41), 179 (8), 165 (23), 149 (5), 125 (8), 124 (4), 123 (6), 109 (5), 83 (4), 75 (6), 70 (8), 69 (6), 68 (5), 58 (5), 57 (5), 55 (7), 43 (5), 41 (11), 29 (3), 18 (22).

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