Organocatalysis

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The Elusive Enamine Intermediate in Proline-Catalyzed Aldol Reactions: NMR Detection, Formation Pathway, and Stabilization Trends**

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Dedicated to Professor Horst Kessler on the occasion of his 70th birthday

The detection and characterization of intermediates in organic reactions is crucial for the understanding of mechanisms and the rational optimization of reaction conditions. However, especially in the rapidly expanding field of asymmetric organocatalysis,[1–4] mechanistic studies are scarce compared to new synthetic applications. Therefore, organocatalysis was characterized as still being "in its exploratory discovery phase before it can become contemplating".[5] Among the different organocatalytic activation modes and the wide range of identified general concepts,[6,7] Brønsted acid[8,9] and Lewis base catalysis[10] have proven to be broadly applicable. After the proline-catalyzed aldol reactions (both origin[11,12] and prototype[13] for asymmetric aminocatalysis), secondary amines[14–16] are preferentially employed to activate substrates via iminium[17] or enamine intermediates.[18] The generally accepted mechanism of enamine catalysis[14,19] is based upon experimental[20] and theoretical studies[21] that suggest a central enamine intermediate in the proline-catalyzed reactions.

To the best of our knowledge, such enamine intermediates have never been detected in situ; only product enamines[22,23] or dienamines,[24] and dienamine intermediates[25] have been reported—for different catalysts. In contrast, putative enamine intermediates were synthesized, isolated, and characterized,[5,26–28] and recently an enamine intermediate was observed in the crystal structure of an aldolase antibody.[29] So far, in situ NMR spectroscopic approaches have only resulted in the detection of the isomeric oxazolidinones,[20,30–34] supposedly resulting from an "unwanted and rate-diminishing parasitic equilibrium",[20,35] which was believed to be responsible for the inability to observe the enamines. In fact, equilibria involving oxazolidinones have been reported[20,32–34] and their energetic preference has been calculated.[36] An alternate mechanistic model of proline-catalyzed aldol reactions that attributes a pivotal role to the predominant oxazolidinones has been proposed,[33] and indeed such oxazolidinones have successfully been used as "soluble proline catalysts".[31–34]

The detection of enamine intermediates in proline-catalyzed aldol reactions is the missing piece of evidence for the commonly accepted mechanism of enamine catalysis. Moreover, the structural characterization of key enamine intermediates, the elucidation of their formation, and their stabilization are important for a better understanding of and the control of organocatalytic reactions, which could in turn present new options in accelerating and controlling enamine-catalyzed reactions.

Herein we present our real-time NMR studies that detail the first detection and structural characterization of enamine intermediates in proline-catalyzed aldol reactions. In addition, their direct formation from oxazolidinones is evidenced in the solvent dimethylsulfoxide (DMSO). Moreover, the influences of the carbonyl species, its substitution pattern, as well as the effect of the solvent and its water content upon the detectable enamine concentration are demonstrated.

The self-aldolization of propionaldehyde (**1**; $c = 50$ mM), catalyzed by 20 mol% L-proline, in [D_6]DMSO at 300 K (Figure 1a) was used as a model reaction in our enamine studies. The reaction was conducted within an NMR tube and monitored by one-dimensional ^{1}H NMR spectra (Figure 1b). Two diastereomeric aldol dimers **2a** and **2b**, and the condensation product **3** were observed, which is in accord with previous studies.[37,38] In addition, three intermediate species were detected, each of which disappeared at identical rates (Figure 1c). By employing 100 mol% L-proline (which led to an acceleration of the reaction and the predominant formation of the condensation product **3**, possibly through a Mannich-like mechanism[39,40]), we successfully increased the total amount of the intermediates from about 8% to 25–30% without changing their relative ratios (see the Supporting Information). This increased amount of the intermediates allowed unambiguous identification and full characterization of these species as the enamine **5** and the two diastereomeric oxazolidinones **4a** and **4b** (in a ratio of about 3.8:1) by using real-time homo- and heteronuclear two-dimensional NMR spectroscopy during the reaction (see the Supporting Information for the complete NMR assignments).

The detection of the ene unit of **5** is rather straightforward due to characteristic ^{1}H chemical shifts and multiplet patterns (Figure 2b). The connection of the ene unit to the proline

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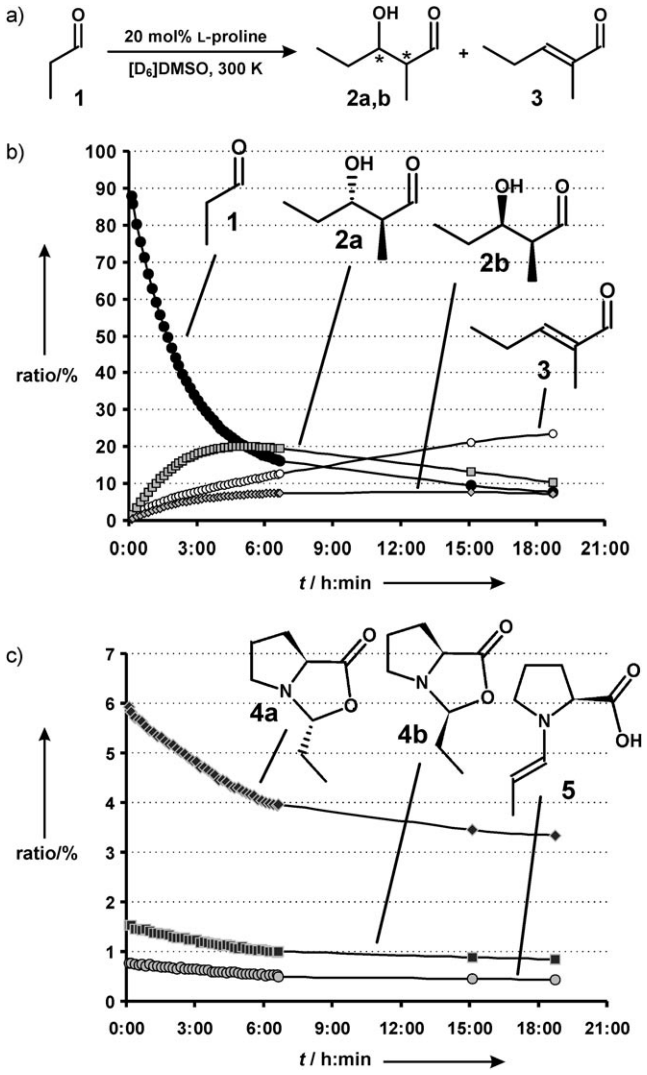


Figure 1. a) L-Proline-catalyzed self-aldolization of propionaldehyde (**1**). Reaction profile of substrate and products (b) and of intermediates (c) as monitored by integration of selected NMR resonances in one-dimensional ^{1}H NMR spectra. Note: The total amount of C_3 moieties stemming from **1**, detected in the first spectrum, was set to 100%.

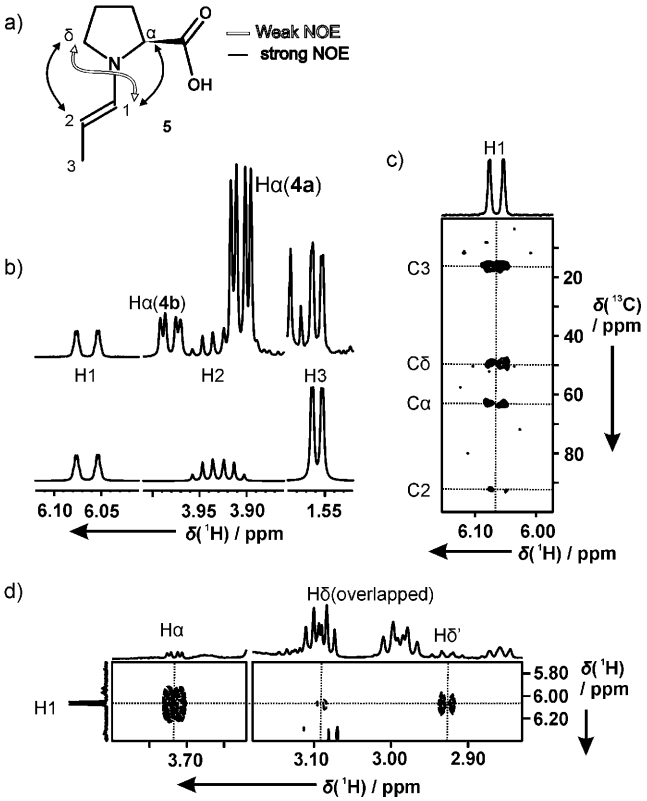


Figure 2. NMR spectroscopic characterization of **5**: a) nomenclature and NOE pattern; b) sections of the ^{1}H NMR spectra (top: experimental, bottom: simulated) of the ene spin system; c) section of a ^{1}H,^{13}C HMBC spectrum revealing through-bond correlations from H1 to Cα and Cδ; d) sections of a ^{1}H,^{1}H NOESY spectrum showing through-space correlations between proton H1 and Hα and Hδ,Hδ′.

residue is proven by through-bond correlations (^{1}H,^{13}C HMBC spectrum; Figure 2c) of H1 to Cα and Cδ, thereby ruling out the existence of a potential enol that was recently suggested for a different but related organocatalyst.[41,42] This finding is additionally supported by through-space correlations (^{1}H,^{1}H NOESY spectrum; Figure 2a and d) of H1 and H2 to Hα and Hδ.

In addition, our spectroscopic results allow the stereochemical characterization of enamine **5**. The size of the scalar coupling constant of H1 and H2 ($^3J_{H1,H2} = 13.7$ Hz) is indicative of an *E* configuration for the enamine double bond. The *Z* isomer was not detected, even at higher *E*-enamine concentrations (see below). Concerning the conformation of the exocyclic N–C bond, the NOESY cross-peak pattern indicates an s-*trans* arrangement since the NOE between H1 and Hα is much larger than those between H1 and Hδ,Hδ′ (Figure 2d). This interpretation is supported by the slightly more intensive HMBC cross-peak between H1 and Cδ compared to Cα (Figure 2c). The finding of an s-*trans* *E* enamine is in agreement with reports on a crystal structure[5] and DFT calculations[28] of an aldehyde-derived enamine of a prolinol ether-type catalyst, and the generally accepted mechanism of enamine catalysis.[20]

Having both oxazolidinones and an enamine intermediate at hand, we investigated the "parasitic equilibrium"[20] and the associated reaction pathways by NMR exchange spectroscopy (EXSY). By tracking the reaction of **1** and L-proline (see EXSY trace for the resonance of **1** in Figure 3a), two exchange cross-peaks, of almost equal intensity, for the isomeric oxazolidinones **4a** and **4b** indicate similar formation rates. Interestingly, in contrast, no exchange peak between **1** and **5**, which would reveal the formation of **5** from **1** and proline, was detected under these experimental conditions. The EXSY trace for the resonance of **4a** (example for both **4a** and **4b**; Figure 3a) indicates a significantly faster exchange between **4a** and **4b** than that between the other species, which may account for the thermodynamic equilibration between **4a** and **4b**. A cross-peak to **1** shows the reverse reaction. In addition and despite the low amounts of the intermediates, exchange peaks between **4a** and **5** as well as **4b** and **5** are

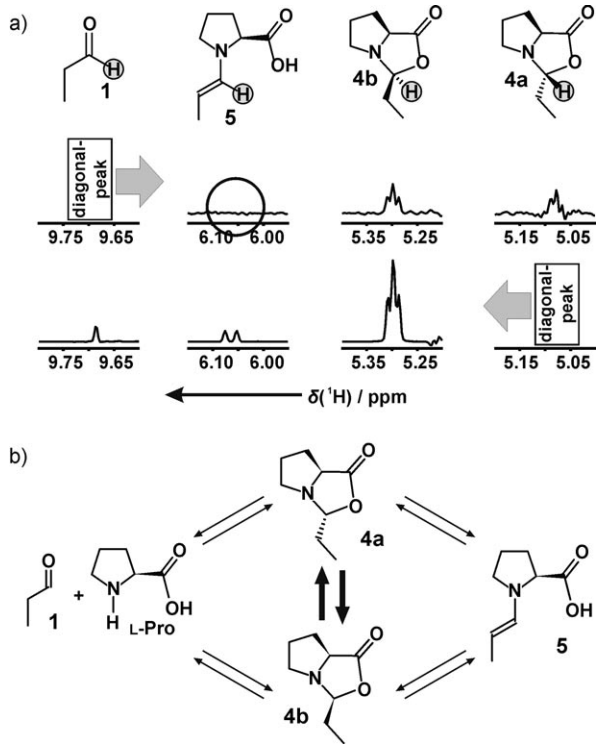


Figure 3. Experimentally detected exchange processes of a propionaldehyde/L-Pro reaction mixture by EXSY methods: a) rows from the ^{1}H,^{1}H EXSY spectrum for the protons of **1** (top) and **4a** (bottom), highlighted in gray, showing exchange peaks to the protons of **1** ($\delta = 9.69$ ppm), **5** ($\delta = 6.06$ ppm), **4b** ($\delta = 5.30$ ppm), and **4a** ($\delta = 5.08$ ppm), and the missing exchange between **1** and **5** (circle; diagonal peaks are omitted for clarity); b) schematic summary of the exchange processes and the qualitative exchange intensities detected by EXSY spectra.

detected. The observed exchange matrix is schematically summarized in Figure 3b.

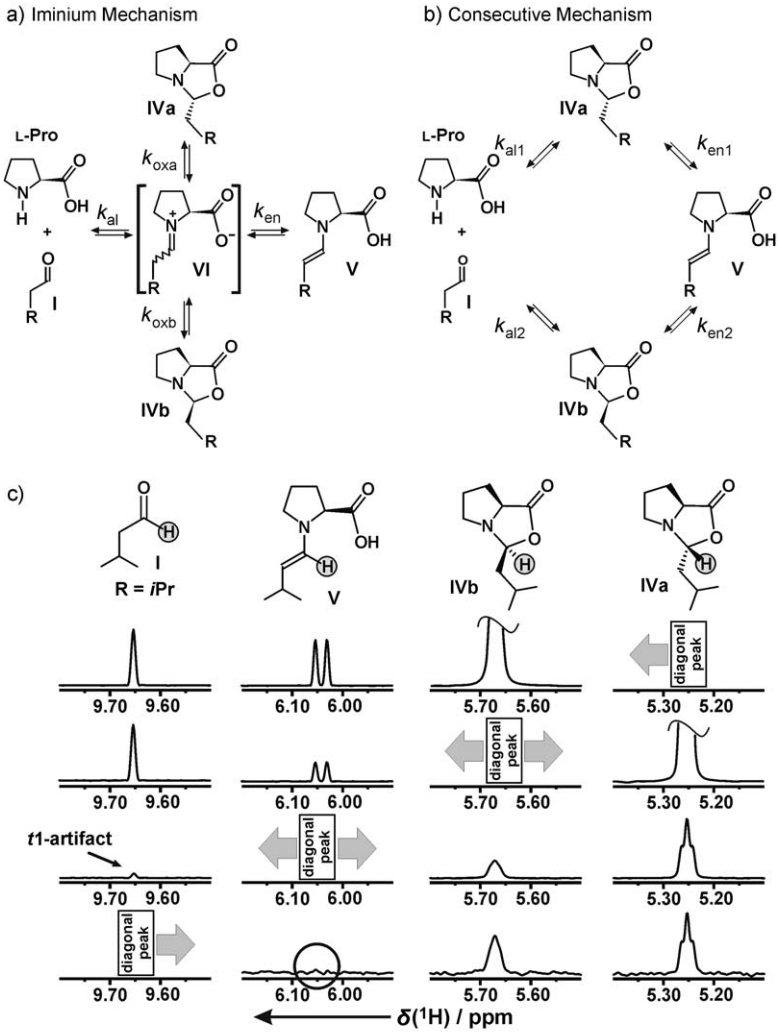
For the enamine formation from aldehydes as well as from oxazolidinones, mechanisms proceeding via iminium intermediates have been proposed[14,33,43] wherein a central iminium species would be responsible for the interconversion between aldehydes, enamines, and oxazolidinones (Figure 4a). The iminium species **VI** is not detected by the NMR methods herein, therefore its structure cannot be identified and, in addition, the existence of various rapidly interconverting iminium and/or carbinolamine species seems possible. However, the fast exchange between the two diastereomeric oxazolidinones **IVa** and **IVb** (Figure 3a and 4c) shows that the interconversion of different putative intermediate species has to be fast compared to either enamine or aldehyde formation. Therefore, for the sake of clarity in Figure 4a only the iminium **VI** is depicted and mentioned hereafter. Surprisingly and in contrast to this commonly assumed iminium pathway, the missing cross-peak between aldehyde **I** and enamine **V** indicates that **V** is formed not via an iminium intermediate **VI** from aldehyde **I**, but directly from the oxazolidinones **IVab**. For such a direct formation of enamines from oxazolidinones a concerted E2 mechanism has recently been proposed,[33] and this reaction pathway would be expected to have different enamine formation rates depending upon the starting oxazolidinone (Figure 4b).

To rule out the possibility that the missing EXSY cross-peak between **I** and **V** is simply below the detection limit, additional positive evidence for the direct enamine–oxazolidinone conversion was collected from our EXSY spectra: For the iminium mechanism (Figure 4a), the aldehyde **I**, the oxazolidinones **IVa** and **IVb**, and the enamine **V** should all interconvert through the central iminium intermediate **VI**, and each species should be formed from this iminium at a distinct rate. By using ratios of these formation rates, for example, the volume of the EXSY cross-peak **IVa**→**I** divided by the volume of the EXSY cross-peak **IVa**→**V**, the contribution of **IVa** is cancelled and a value of the relative rates k_{al}/k_{en} is obtained. This value should be independent of how the central intermediate was formed (e.g., starting from either **IVa** or **IVb**). Therefore, in the case of a common iminium intermediate **VI**, the resulting ratios of the formation rate should be nearly identical [Eq. (1)].

$$\frac{\mathbf{IVa} \rightarrow \mathbf{I}}{\mathbf{IVa} \rightarrow \mathbf{V}} \approx \frac{\mathbf{IVb} \rightarrow \mathbf{I}}{\mathbf{IVb} \rightarrow \mathbf{V}} \approx \frac{k_{al}}{k_{en}} \quad (1)$$

In contrast, significant differences in these ratios would exclude a common central intermediate or a pool of rapidly interconverting intermediates, and instead provide evidence for the direct formation of the enamine **V** from the oxazolidinones **IVa**,**b** (Figure 4b). To apply this key differentiator to the two exchange pathways discussed, the ratios of the crucial EXSY cross-peak volumes were calculated for three different reaction mixtures each derived from a different aldehyde (Figure 4d; representative EXSY traces are shown for 3-methyl-butyraldehyde in Figure 4c). For all pairs of EXSY cross-peak ratios significantly different volume ratios, that is, formation-rate ratios (by factors of 2.5 to 5) are obtained. These values indicate that the enamine **V** is indeed formed directly from the oxazolidinones **IVa**,**b** (Figure 4b) under the experimental conditions used, and excludes in this process the presence of a common central intermediate or a pool of rapidly interconverting intermediates such as the commonly proposed iminium ion.

In view of these intermediate equilibria, we investigated the influence of the amount of catalyst, the water content of the sample, the solvent properties, and the substitution pattern of the carbonyl compound upon the appearance and the relative ratios of oxazolidinones and enamines. First, we showed that for the reaction depicted in Figure 1a, increasing the amount of catalyst from 20 mol% to 100 mol% leads to higher concentrations of the intermediates, but does not alter their equilibrium ratios (see the Supporting Information). Therefore, all experiments discussed hereafter were performed at substrate concentrations of 50 mM with 100 mol% L-proline. Next, the influence of the amount of water upon the overall intermediate concentration and the relative ratios of the intermediates **4a**, **4b**, and **5** was investigated using **1** and 3-methyl-butyraldehyde because the latter had the highest enamine amount (see Table 2 and discussion below). A stepwise increase of the water content led to a reduction of



d)

ratios of EXSY crosspeak volumes		
R	$\frac{IVa \rightarrow I}{IVa \rightarrow V}$	$\frac{IVb \rightarrow I}{IVb \rightarrow V}$
Me	0.5[a]	2.5[a]
Et	1.1	4.4
*i*Pr	0.7	1.8

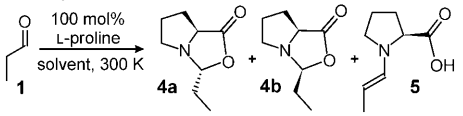
Figure 4. Differentiation between alternative enamine formation pathways by analysis of EXSY cross-peak ratios: a) previously proposed mechanism with a central iminium intermediate or a pool of rapidly interconverting intermediates (see text); b) experimentally confirmed direct enamine formation from oxazolidinones; c) relevant sections of the ^{1}H,^{1}H EXSY spectrum of a 3-methylbutyraldehyde/L-Pro mixture for the highlighted ^{1}H resonances; d) quantitative evaluation of the 2D EXSY cross-peaks for different aldehydes: the different ratios of the formation rates disprove the presence of a central intermediate as depicted in (a). [a] Ratio determined by integration of the peaks in the 1D EXSY trace.

the overall amount of the intermediates present until their detection limit was reached at around 15 vol% of water in DMSO (for details see the Supporting Information). This result is in agreement with previous reports on the reduction of the amount of oxazolidinone upon the addition of water,[44,45] as well as with their reversible formation by condensation. Interestingly, the relative ratios of the intermediates **4a**, **4b**, and **5** remain unaffected up to about 2 vol% of water (limit of a reliable relative integration, see the Supporting Information). This suggests that the solvent properties responsible for the relative stabilization of **4a**, **4b**, and **5** do not change significantly in these solvent mixtures—at least on the level of microsolvation. In addition, a severe line broadening of the oxazolidinone signals and changes in the chemical shifts of the oxazolidinones and the aldehydes are observed with increasing water content, whereas the line widths and the chemical shifts of the enamine signals remain essentially unaffected (see the Supporting Information). This corroborates the equilibria presented in Figures 3b and 4b showing the formation of the oxazolidinones from aldehydes and proline, and then a subsequent step for the formation of the enamines under the experimental conditions applied.

Secondly, we were interested in the extent to which the amount of the enamine is influenced by solvent properties. In addition to [D$_6$]DMSO, we repeated the self-aldolization of **1** in other protic and dipolar aprotic organic solvents that are successfully used in proline-catalyzed reactions ([D$_3$]MeCN, [D$_7$]DMF, and [D$_4$]MeOH). The results as well as relevant solvent parameters are summarized in Table 1. In DMF, just as in DMSO, all three intermediates **4a**, **4b**, and **5** were detected, however, the amount of **5** was reduced from 9% to 4% and the reaction is considerably slower. In MeCN the reaction was very slow and only **4a** and **4b** were detected, whereas in [D$_4$]MeOH the reaction proceeded quickly, such that no intermediates could be identified. A correlation of the amount of **5** to the parameters of the respective solvents[46,47] reveals that their hydrogen-bond donor (α) and acceptor (β) ability, and not their dielectric constant (ε), are crucial for the relative enamine amount. DMSO and DMF, having $\alpha = 0$, allow for enamine detection and the amount of enamine correlates with the respective β values of DMSO and DMF. In MeCN, which has a poor β value (and, in addition, low α value), only oxazolidinones are observed; this data is in good agreement with reports on optimal oxazolidinone yields in MeCN.[30] In contrast, for the dipolar protic solvent MeOH that possesses a β value similar to that of DMSO and DMF, and a high α value, no enamines are detected. Therefore, both a high β value and a low α value together are favorable for enamine stabilization.

Our experimental observations suggest that the stabilization of the carboxylic proton in the proline-enamine species by solvents having high β values decreases the collapse of the enamine into the oxazolidinone and is therefore crucial for the detectability of enamines. The exquisite capability of

Table 1: Selected solvent properties and their influence upon the relative ratios of the intermediates **4a**, **4b**, and **5** (total amount of intermediates was set to 100%).[a]



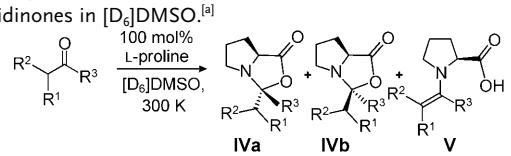
Solvent	ε_r	α	β	**4a** [%]	**4b** [%]	**5** [%]
[D_6]DMSO	46.5	0.00	0.76	72	19	9
[D_7]DMF	37.8	0.00	0.69	77	19	4
[D_3]MeCN	35.9	0.19	0.40	80	20	n.d.
[D_4]MeOH	32.7	0.98	0.66	n.d.	n.d.	n.d.

[a] n.d. = not detected; ε_r = dielectric constant; α,β = Kamlet–Taft parameters characterizing hydrogen-bond donor and acceptor ability, respectively.

DMSO to form complexes with hydroxy groups was recently explored by means of a 3-hydroxyflavone (3HF) which, upon undergoing intermolecular proton transfer, forms a $3HF^{-}{\cdot}DMSOH^{+}$ complex.[48] Experimental findings suggest that DMF follows this trend better than MeCN.[48–50] To verify such an interaction between **5** and DMSO, we used diffusion-ordered spectroscopy (DOSY) and found significantly slower diffusion of **5** compared to that of **4a** and **4b** (see the Supporting Information); this result cannot be simply explained by the different shapes of the molecules, but instead we believe this to be indicative of "strong interactions" between the carboxy group of **5** and solvent molecules.

Furthermore, we studied the influence of different substitution patterns of the carbonyl compound upon the amount of enamine observed (Table 2). First, enamine detection was successful only for aldehydes, and not for ketones: Butanone (Table 2, entry 1) did not form any adduct with L-proline under our experimental conditions, whereas for acetone (Table 2, entry 2), only the oxazolidinone was observed, which is in agreement with previous NMR studies.[20] In both cases, neither an enamine intermediate nor a reaction was observed. This result may be rationalized by the lower carbonyl activity of ketones compared to aldehydes, and by the preference of ketone-derived oxazolidinones as anticipated by the Thorpe–Ingold effect.[51,52]

Table 2: Influence of the carbonyl species and its substitution pattern upon the preference of the equilibrium between the enamine and the oxazolidinones in [D_6]DMSO.[a]



Entry	R^1	R^2	R^3	**IVa** [%]	**IVb** [%]	**V** [%]
1	Me	H	Me	n.d.	n.d.	n.d.
2	H	H	Me	----- 100% -----		n.d.
3	H	H	H	n.d.	n.d.	n.d.
4	Me	Me	H	90	9	1
5	Me	H	H	72	19	9
6	Et	H	H	64	23	13
7	*i*Pr	H	H	57	23	20

[a] n.d. = not detected.

Next, starting from **1**, we investigated the influence of α- and β-alkyl substituents on the aldehyde upon the relative ratios of oxazolidinones and enamines. For acetaldehyde (Table 2, entry 3), self-aldolization was so fast that among a variety of intermediates and products only the dienamine could be identified. In contrast, for isobutyraldehyde (Table 2, entry 4) no product formation was observed and only tiny amounts of enamine were detected, thereby suggesting—as has already been reported[30]—α-substitution on the aldehyde favors oxazolidinones instead of enamines, probably because of the presence of the unfavorable allylic strain in the enamine which is more predominant than the stabilization of the double-bond by higher alkyl substitution. For butyraldehyde (Table 2, entry 6) higher enamine ratios than those for propionaldehyde (**1**; Table 2, entry 5) were detected, and can be ascribed to the stronger +I- and hyperconjugation effects of the ethyl group. Additional alkyl substitution in the β position, as shown for 3-methylbutyraldehyde (Table 2, entry 7), leads to an additional increase of the enamine ratio which might be accounted for by further +I-effects and a reduced reactivity resulting from steric crowding.

On the basis of the NMR detection and characterization of reaction intermediates, and the observation of the reaction pathways by EXSY methods (see Figure 3 and 4 and the Supporting Information), we propose a slightly modified mechanism of proline-catalyzed aldol reactions in dipolar aprotic solvents exclusively having hydrogen-bond acceptor properties (Figure 5). First, oxazolidinones **4** are formed from **1** and L-proline, probably via the commonly proposed iminium intermediate **6**, which also allows the rapid isomerization of **4a** and **4b**. The extremely short lifetime of **6** resulting from its immediate collapse into **4a,b** may account for the inability to detect iminium ion **6** in our study, and can be rationalized by the poor solvation capability of DMSO towards anionic species,[53] that is, the carboxylate moiety. Next, the s-*trans* *E*-enamine **5** is formed directly from **4a** and **4b**, as evidenced by EXSY analysis. For such a direct transformation of oxazolidinones into enamines, Seebach et al. recently proposed a concerted E2 mechanism.[33] The latter steps of the reaction are mostly in agreement with the generally accepted mechanism of enamine catalysis.[14,19] We speculate that two very small intermediate peaks, slightly upfield shifted from those of **2a,b**, belong to the iminium species **7** (see the Supporting Information) formed by C–C bond formation between **5** and **1**. Subsequently, product oxazolidinones **8** are observed and in the final step the catalyst is released by hydrolysis to **2a,b**.

In summary, the first in situ detection of enamine intermediates in proline-catalyzed aldol reactions, accomplished by using NMR methods, is reported and new insights into the stabilization and the formation pathway of enamines in dipolar aprotic solvents are presented. Exclusively *E*-configured s-*trans* enamines are detected; in DMSO, these enamines are formed directly from oxazolidinones and not via central iminium or iminium-like intermediates as evidenced by EXSY analyses. The position of these oxazolidinone-enamine equilibria is not affected by additional water

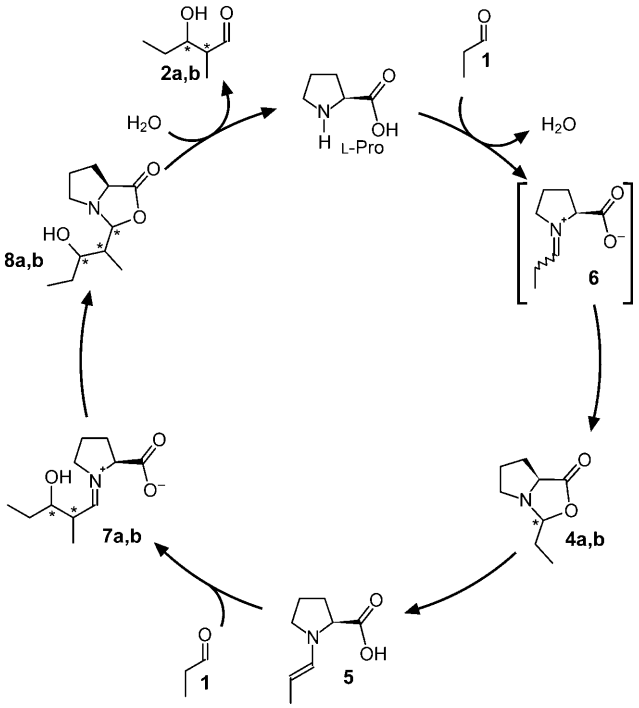


Figure 5. Proposal for the catalytic cycle of proline-catalyzed aldol reactions in dipolar aprotic solvents based on NMR-detected intermediates and exchange pathways (the equilibrium arrows are omitted for clarity).

or the amount of the catalyst. The presence of strong hydrogen-bond acceptor properties together with the absence of hydrogen-bond donor properties of the solvent increase the amount of enamine present. Ketones and α-branched aldehydes show no or very low enamine concentrations, whereas β-alkyl substituents of propionaldehydes cause enamine stabilization. Our results corroborate not only the central role of enamines in proline-catalyzed aldol reactions, but also elucidate a new role of the oxazolidinones as a bridge between aldehydes and enamines in dipolar aprotic solvents. In conclusion, the first detailed insights into the oxazolidinone-enamine conversion processes presented herein should allow rational and directed optimizations of proline-catalyzed reactions.

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