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Formation and Stability of Prolinol and Prolinol Ether Enamines by NMR: Delicate Selectivity and Reactivity Balances and Parasitic Equilibria

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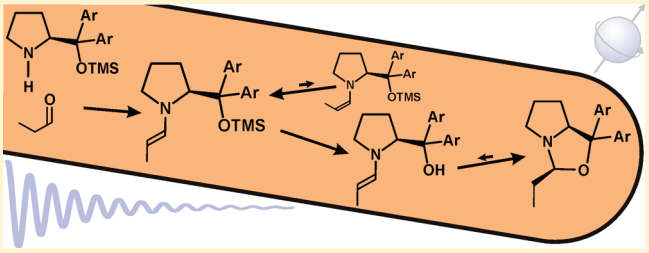
Supporting Information

ABSTRACT: Enamine key intermediates in organocatalysis, derived from aldehydes and prolinol or Jørgensen−Hayashi-type prolinol ether catalysts, were generated in different solvents and investigated by NMR spectroscopy. Depending on the catalyst structure, trends for their formation and amounts are elucidated. For prolinol catalysts, the first enamine detection in situ is presented and the rapid cyclization of the enamine to the oxazolidine ("parasitic equilibrium") is monitored. In the case of diphenylprolinol, this equilibrium is fully shifted to the *endo*-oxazolidine ("dead end") by the two geminal phenyl rings, most probably because of the Thorpe−Ingold effect. With bulkier and electron-withdrawing aryl rings, however, the enamine is stabilized relative to the oxazolidine, allowing for the parallel detection of the enamine and the oxazolidine. In the case of prolinol ethers, the enamine amounts decrease with increasing sizes of the aryl meta-substituents and the *O*-protecting group. In addition, for small aldehyde alkyl chains, *Z*-configured enamines are observed for the first time in solution. Prolinol silyl ether enamines are evidenced to undergo slow desilylation and subsequent rapid oxazolidine formation in DMSO. For unfortunate combinations of aldehydes, catalysts, solvents, and additives, the enamine formation is drastically decelerated but can be screened for by a rapid and facile NMR approach. Altogether, especially by clarifying the delicate balances of catalyst selectivity and reactivity, our NMR spectroscopic findings can be expected to substantially aid synthetically working organic chemists in the optimization of organocatalytic reaction conditions and of prolinol (ether) substitution patterns for enamine catalysis.



INTRODUCTION

Detailed knowledge on the formation and the stability of intermediate species is essential for an improved understanding and hence control of organic reactions. Especially in the increasingly important and still rapidly growing field of modern asymmetric organocatalysis,[1−5] detailed mechanistic insights into intermediate properties should largely facilitate the development of novel catalytic systems and the optimization of reaction conditions. As one of the most successfully and widely applicable principles of modern organocatalysis, enamine catalysis by secondary amines, typically originating from the chiral pool,[6−10] has emerged to an extension of the original proline catalysis[11−13] in recent years. Among a variety of different catalyst scaffolds, in particular Jørgensen−Hayashi-type prolinol ethers[14−19] have demonstrated excellent performances in asymmetric enamine organocatalysis, and though a lot less pronouncedly, prolinol-type organocatalysts[20] have also found applications based on enamine intermediates.[21−24]

Still, in view of the vast number of synthetic applications, studies on the mechanistic understanding of enamine catalysis must be termed insufficient.[25] While computational studies have proven to be very useful for the prediction of stereoselectivities,[26] knowledge on the appearance of active reaction intermediates is often poor. Only recently we could detect and characterize in situ the first enamine intermediate[27] in the archetypical proline-catalyzed intermolecular aldol reaction.[13] At the same time, the first crystal structure of an enamine intermediate in an aldolase antibody was reported.[28] Nevertheless, to our knowledge, not a single prolinol-derived enamine in solution has been reported so far. For prolinol silyl ether-type organocatalysts, on the other hand, two enamines could be isolated and characterized,[29−31] but in situ only one dienamine intermediate[32] and one product enamine[33] have been observed. Hence, very little is known about the formation trends and the stabilities of prolinol- and prolinol ether-derived enamines, even though this information should be highly appreciated by synthetically working organic chemists for the optimization of organocatalytic reaction conditions.

To fill this gap, we designed in situ NMR studies on reactive prolinol and prolinol ether enamines. In this paper, we present the first detailed study on the formation and stability of enamines, derived from aldehydes and prolinol (ether)-type organocatalysts, by means of NMR spectroscopy in solution. Our findings by ^{1}H NMR reaction monitoring reveal trends for the formation

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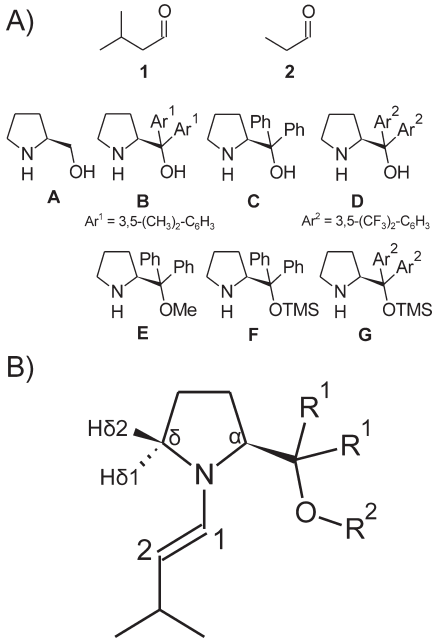
Chart 1. (A) Aldehydes and Organocatalysts Examined in This Study and (B) General Atom Nomenclature Used for Enamines Derived Thereof

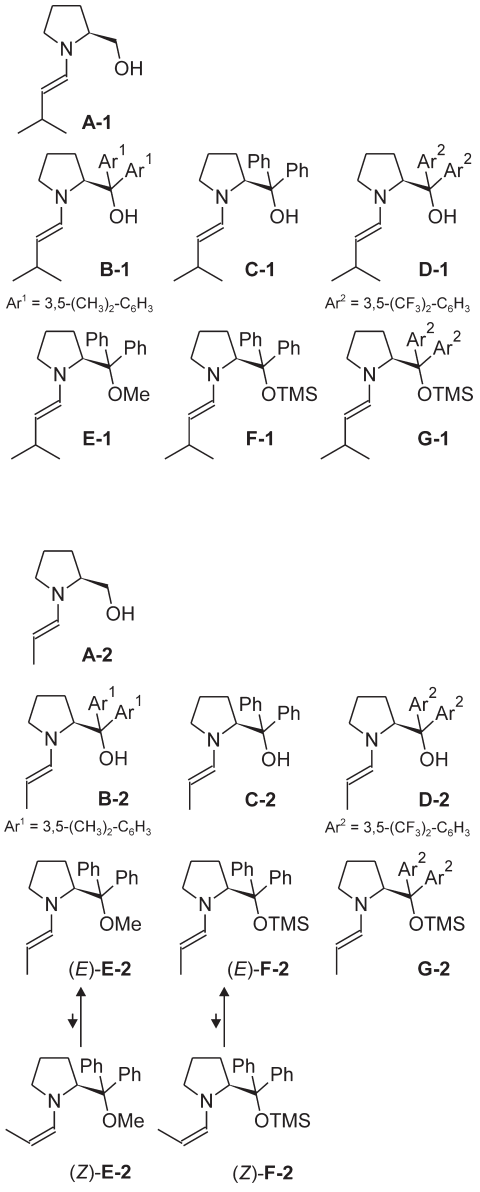


rates of such enamines depending on the catalyst structure and for the amounts of enamine formed. Furthermore, information on the enamine resistance against cleavage of the hydroxyl protecting group and against ring closure to the isomeric oxazolidines ("dead ends") is provided.

RESULTS AND DISCUSSION

Model Enamines. Following the experience from our earlier investigations on proline enamines,[27] mixtures of prolinol (ether)-type organocatalysts and α-unbranched aldehydes (Chart 1) in DMSO were envisaged as the best conditions for achieving sufficient enamine stabilization. Thereby, the observation of prolinol (ether) enamines was furthermore expected to be aided by the well-known fact that, in contrast to proline, prolinol (ether)-type organocatalysts do not promote aldehyde self-aldolizations as readily.[8] Various secondary amines (**A**–**G**),[14−16] derived from proline, that are typically and very successfully used as organocatalysts for enamine catalysis were selected for our studies. They were mixed with two different aldehydes, 3-methylbutyraldehyde (**1**) and propionaldehyde (**2**). Especially, we chose **1** for the enamine formation study as we had found earlier that the unwanted aldehyde self-aldolization of this substrate is minimized even under proline catalysis.[27] Therefore, the superimposition of enamine formation and the potentially subsequent aldol reaction is expected to be less problematic for **1**. By comparison with **2**, the impact of the size of the aldehyde alkyl chain was to be studied. DMSO was used predominantly as the solvent in order to achieve the maximum amounts and stabilities of the enamines, especially in the case of prolinol-type catalysts;[27] the obtained results were then verified for selected other solvents (methanol, acetonitrile, chloroform, dichloromethane, and toluene). All experiments mentioned hereafter (if not stated otherwise) were performed within NMR tubes by mixing

Chart 2. Overview on the Investigated Enamines Derived from Aldehydes 1 and 2 and Catalysts A−G[a]



[a]All enamines are displayed in the (more stable) *s*-trans conformation with respect to the exocyclic N−C bond.

equimolar amounts of aldehyde and catalyst in perdeuterated solvents to obtain concentrations of 50 mmol/L each, and NMR spectra were recorded at 300 K (see Experimental Section for details).

Enamine Detection and NMR Characterization. Overall 14 different enamines formed from the aldehydes **1** and **2** and the organocatalysts **A**–**G** (designated as "catalyst character-aldehyde number", e.g., **A-1**; Chart 2) were obtained in different solvents and investigated in situ (See Charts S1 and S2 in the Supporting Information for full NMR assignments).

The detection of the ene moiety of the enamines was straightforwardly accomplished on the basis of its characteristic resonances in one-dimensional ^{1}H spectra;[27] in particular, the doublet for H1 proved to be characteristic and easily recognizable because of its appearance in the noncrowded spectral region

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between 6.3 and 5.9 ppm. (Only the H1-resonances of the diarylprolinol enamines derived from **B**−**D** appear between 5.42 and 5.20 ppm due to significant ring current effects.[34]) For all aldehyde−amine combinations, the major conformer was evidenced to be *E*-configured at the enamine double bond by their scalar coupling constant $^{3}J_{H1,H2}$ of 13.5−13.9 Hz.[35] In addition, for **E-2** and **F-2**, i.e., for enamines formed in high amounts and bearing a relatively small alkyl chain, the *Z*-configured isomers were detected for the first time besides the *E*-isomers in solution. They are characterized by their upfield-shifted (about 0.2−0.3 ppm relative to the *E*-enamines) H1 doublets of about 8.8 Hz,[35] but they accounted for only about 1.5% of the total enamine amount in DMSO, MeCN, and PhMe. (A putative *Z*-enamine of **D-1** amounting to only 0.4% of the enamine concentration in DMSO could not be verified unambiguously.) Because of their low concentrations, the *Z*-enamines could not be investigated further so far; consequently, we can only speculate whether their presence may actually compromise the selectivity of prolinol ether enamine catalysis. Our experimental detection of the favoring of the *E*-configuration over the *Z*-configuration agrees with other experimental findings reported earlier: the detection of the *E*-configuration for isolated prolinol ether enamines by NMR in solution and by X-ray analyses in the crystal[29,30] and for an in situ prolinol ether dienamine.[32] Our in situ NMR findings on a substantial preference of the *E*-configuration are moreover in good agreement with an empirical estimation of the relative stability of enamine *E*/*Z*-isomers[36,37] and also with the results from theoretical calculations.[30,32,38−41] Nevertheless, examples **E-2** and **F-2** reveal the additional presence of a small amount of *Z*-configured second request for this correction enamines, derived from aldehydes and amine organocatalysts, in solution. For the *E*-enamines, comprehensive homo- and heteronuclear NMR experiments were performed on the example of **F-2** (see Chart S3B in the Supporting Information). Thereby, in analogy to our previous investigations,[27] the covalent connection of the ene unit to the pyrrolidine ring of the catalyst was proven via the $^{1}H,^{13}C$ HMBC by crosspeaks from H1 to Cα and Cδ and vice versa from Hα and Hδ1 to C1, obviously conflicting with a previously calculated enol mechanism.[42] This finding was confirmed by $^{4,5}J_{H,H}$ long-range couplings from H1 and H2 to Hδ1,2, observed in the $^{1}H,^{1}H$-COSY spectrum.

Enamine Stability, Formation, and Degradation. *Prolinol Enamines.* The employment of *O*-unprotected prolinol derivatives[20] in enamine organocatalysis is a lot less common than the corresponding methyl or silyl ethers since, for example in combination with aldehydes, considerable amounts of the catalysts are said to be irreversibly removed from the catalytic cycle by formation of stable oxazolidines (frequently also referred to as hemiaminals).[38] Accordingly, only a few superior applications of prolinol enamines have been reported so far.[21−24] To shed some light on the properties and the behavior of prolinol enamines, we investigated the formation and stability of enamines derived from **1** or **2** and the (diaryl)prolinols **A**−**D**, respectively, i.e., **A-1**, **A-2**, **B-1**, **B-2**, **C-1**, **C-2**, **D-1**, and **D-2**. Similarly to the proline-derived enamines,[27] prolinol enamines could not be detected in MeOH-d_4, MeCN-d_3, $CDCl_3$, or PhMe-d_8 but only in the dipolar aprotic solvent DMSO-d_6, as was tested on the example of diphenylprolinol (**C**). This finding again underlines our previous statement that the stabilizing interaction between solvent molecules with exclusive hydrogen-bond-acceptor properties and the carboxylic/hydroxylic proton of the enamine intermediate may be crucial for the detectability of proline/prolinol enamines in equilibrium with their cyclized oxazolidinone/oxazolidine tautomers.[27] First, by comparison of prolinol (**A**) and diphenylprolinol (**C**), we investigated the general influence of the two geminal phenyl rings on the formation and stability of prolinol enamines. The evolution of the amounts of enamines in the reaction mixtures of aldehydes **1** or **2** and catalysts **A** or **C**, respectively, in DMSO-d_6 is depicted in Figure 1A and B.

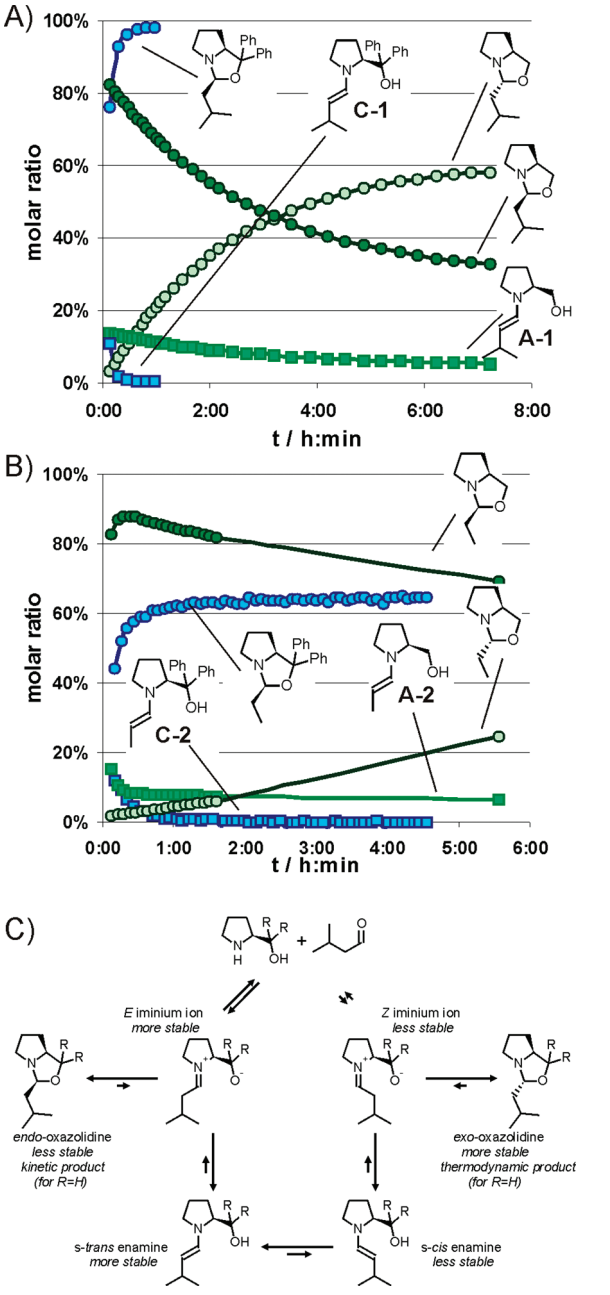

Figure 1. Evolution of the amounts of enamines and oxazolidines derived from the aldehydes **1** (diagram A) and **2** (diagram B) and the prolinol-type organocatalysts **A** (green) and **C** (blue) in DMSO-d_6 over time as monitored by 1D ^{1}H NMR spectroscopy. (Note: The total amount of aldehyde-derived species, detected in the first spectrum, was set to 100%.) (C) Proposed equilibria[38] between the starting material, iminium ions, enamines, and oxazolidines.

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For diphenylprolinol (**C**), only low amounts of the enamines **C-1** and **C-2** (below 20% of all aldehyde-derived species) can be detected in the reaction mixture, and their observation by NMR is temporally restricted to the first 1.5 h, since their amounts decrease rapidly and the isomeric oxazolidine is in fact formed almost quantitatively (Figure 1A,B).[38] Only the *endo*-oxazolidine (with the proline side chain and the aldehyde alkyl chain in the same half-space of the oxazolidine ring; see Figure 1C) is observed;[43] this is in agreement with previous findings on the preferred oxazolidine formation of diphenylprolinol (**C**).[44,45] For prolinol (**A**), on the other hand, the enamines **A-1** and **A-2** and the corresponding kinetic *endo*-oxazolidines are found in the beginning, too, but the enamines do not disappear in favor of the *endo*-oxazolidines during the time interval observed. Instead, the *endo*-oxazolidine and the enamine amounts decrease in parallel at a constant ratio of about 6:1 in the case of aldehyde **1** and of about 11:1 in the case of **2** (after an induction period of about 30 min) throughout the observation period. In turn, along with the vanishing of the *endo*-oxazolidine and the enamine, the thermodynamically favorable *exo*-oxazolidine appears, and its molar ratio increases over time and approaches asymptotically a constant value of about 60% in the case of aldehyde **1**. Thereby, the formation rate of the *exo*-oxazolidine (Figure 1A) is the highest when the concentration of the *endo*-oxazolidine and the enamine is the highest, i.e., in the beginning of the reaction. Similarly for propionaldehyde (**2**), the eventual formation of the *exo*-oxazolidine is observed, but its amount increases substantially slower than in the case of **1**.

For prolinol (**A**), the parallel decrease of the concentrations of the *endo*-oxazolidines and the corresponding enamines indicates that there is a rapid equilibration between these tautomeric species (possibly via the commonly proposed iminium ions; Figure 1C)[38] and that the oxazolidine formation is hence reversible (similarly to the enamine−oxazolidinone equilibrium as in the case of proline catalysis).[27] This interpretation is backed experimentally by an EXSY cross-peak from the *endo*-oxazolidine, formed from amine **A** and propanal (**2**), to the enamine **A-2** (data not shown). Most notably, however, in striking contrast to the direct enamine formation from oxazolidinones in proline catalysis in DMSO,[27] the vanishing of the diphenylprolinol-derived enamines **C-1** and **C-2** in favor of the *endo*-oxazolidines (Figure 1A and B) clearly reveals that the enamines are *not* formed directly from the oxazolidines. Hence, the commonly postulated equilibria including the hypothetical iminium ions (Figure 1C)[38] may well be justified in the case of diarylprolinol−aldehyde adducts. Comparing the enamines **A-1** and **A-2** in their equilibria with the *endo*-oxazolidines, the lower ratio *endo*-oxazolidine:enamine in the case of **1** may be rationalized thermodynamically by the steric destabilization of the *endo*-oxazolidine and the inductive stabilization of the enamine owing to the larger aldehyde alkyl chain present in **1** (isopropyl residue) than in **2** (methyl residue). Starting from this rapid exchange between the *endo*-oxazolidine and the enamine in the case of prolinol (**A**), the thermodynamic equilibrium between these two species and the *exo*-oxazolidine is slowly established. For this eventual formation of the thermodynamic *exo*-oxazolidine, the iminium ion *E*/*Z* isomerization (Figure 1C) has to occur either directly, via the starting aldehyde, via putative carbinolamines, or via the *s*-cis/*s*-trans isomerization of the enamine species. However, in our reaction mixture of **A** and aldehydes **1** and **2** in DMSO, neither iminium ions nor carbinolamines were detected and only tiny amounts of the free aldehyde (far below 1%) so that these species can hardly be expected to provide sufficient amounts of the thermodynamically unfavorable *Z* iminium ion for the substantial formation of the *exo*-oxazolidine. Instead, the enamines are readily observed and the maximum concentration of **A-1** corresponds well to the maximum formation rate of the *exo*-oxazolidine. Moreover, in a parallel study, we could evidence on the example of **A-2** for the first time a significant population of the *s-cis*-enamine conformation.[34] In addition, the *s*-trans/*s*-cis equilibration must be fast, since only one enamine signal set is observed NMR spectroscopically.[34] Altogether, these findings strongly suggest that the thermodynamic *exo*-oxazolidine is formed from its kinetic endo isomer mainly via ring-opening to the enamine, *s*-cis/*s*-trans isomerization on the enamine stage, and subsequent ring closure. On this basis, the faster formation of the exo-isomer in the case of aldehyde **1** may be explained by the stronger steric repulsion in the *endo*-oxazolidine of **1** compared to **2**, which facilitates the ring-opening reaction to the enamine.

In contrast to **A**, for diphenylprolinol (**C**), the enamines **C-1** and **C-2** rapidly vanish in favor of the *endo*-oxazolidine, and no *exo*-oxazolidines are detected. Considering the small structural difference between **C** and **A**, the strikingly higher stability of the *endo*-oxazolidine derived from **C** is rather surprising. The experimental discrepancies between catalysts **A** and **C** must hence be attributed to the impact of the two geminal phenyl rings present in the diphenylprolinol (**C**) only, namely, to their steric demand and to the well-known Thorpe−Ingold effect.[46,47] In line with our assumptions in a previous study[27] on proline enamines, this structural motif promotes the ring closure to the *endo*-oxazolidine and moreover stabilizes the oxazolidine ring, once formed, thermodynamically, as evidenced by the absence of the enamines **C-1** and **C-2** after more than 1.5 h. The inability to detect the exo-isomer in the case of **C** suggests, in combination with the low ability of DMSO to stabilize anions,[48] that this effect is as strong as that of the lifetime of the open-chain species (iminium ion and enamine) and/or that the extent of the oxazolidine ring-opening is insufficient to allow for an isomerization process between the oxazolidines; this might also be reflected by the inability to detect iminium species in our study. Thus, the conversion of the *endo*-oxazolidine to the exo form is unfeasible for **C**, since it would need to proceed via an open-chain intermediate. In contrast, the *endo*-oxazolidine derived from **1** or **2**, respectively, and catalyst **A**, being devoid of the geminal phenyl rings, is less stabilized and thus opens more easily. This leads to the enamine for which, because of the lower steric demand of the CH_2OH-moiety in **A**, the thermodynamic preference of the *s-trans*-enamines over the *s-cis*-enamines (likewise the preference of the *E* over the *Z* iminium ion) is lower than in the case of **C**.[29,30,32,38−40] This allows the easy population of the *s*-cis conformation[31] and hence the formation of the *exo*-oxazolidines. Most interestingly, the in situ observation of higher enamine concentrations in the case of **A** in comparison to **C** as well as the suggested *s*-cis/*s*-trans isomerization of the enamine are also in good agreement with the typical performances of **A** and **C** in enamine catalysis: Higher reactivities are reported for **A** but better selectivities for **C**.[49−52]

However, the overall performance of **C** as an organocatalyst for aldol reactions is very poor. This can now be rationalized for the first time on an experimental basis by the lack of reasonable amounts of enamine over a sufficiently long time. In contrast, different diarylprolinol organocatalysts with substituted phenyl rings, for instance the di-*m*-methyl- or di-*m*-trifluoromethyl-substituted analogs **B** and **D**, have demonstrated substantially

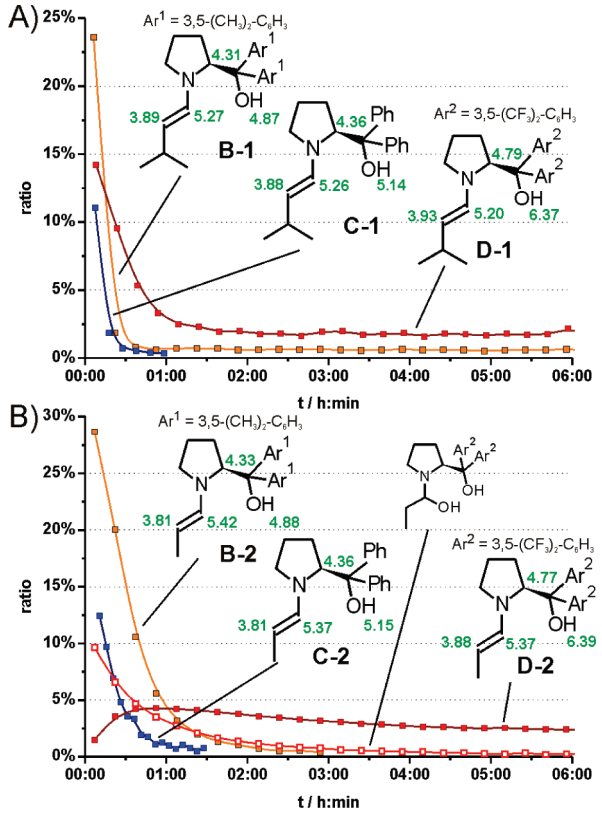


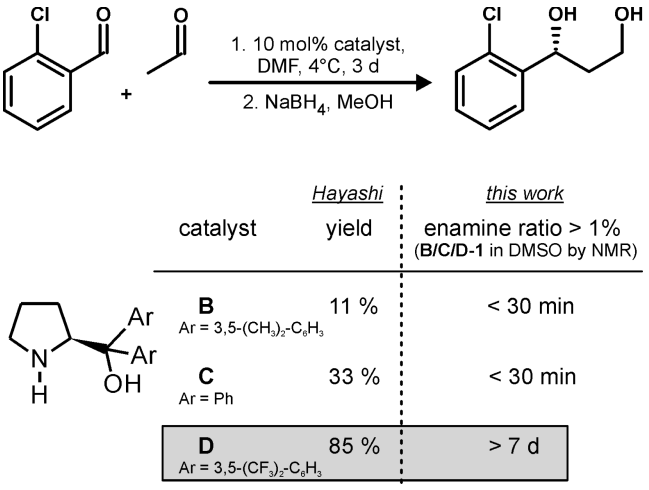
Figure 2. Evolution of the amounts of enamines derived from the aldehydes **1** (A) and **2** (B) and the diarylprolinol-type organocatalysts **B** (orange), **C** (blue), and **D** (red) in DMSO-d_6 at 300 K over time as monitored by 1D ^{1}H NMR spectroscopy. (Note: The total amount of aldehyde-derived species, detected in the first spectrum, was set to 100%.) Relevant ^{1}H chemical shifts (in ppm) are given in green.

better catalytic properties in promoting aldol reactions.[23,24] Most interestingly, reaction times of several days are reported for these prolinol-catalyzed reactions, which is in seeming contradiction to the disappearance of the diphenylprolinol enamines **C-1** and **C-2** within less than 2 h in DMSO. To shed more light on this issue of prolinol enamine catalysis, the formation and stability of enamines derived from the aldehydes **1** and **2** and the diarylprolinols **B**−**D** were investigated. The choice of **B** and **D** with phenyl substituents of similar sizes (CH_3 and CF_3) but with different electron demands (electron release by CH_3 and electron withdrawal by CF_3) should, by comparison with **C**, allow one to identify and to distinguish steric and electronic contributions to the relative enamine stabilization with respect to the isomeric *endo*-oxazolidines. On the one hand, the increased size of the aryl substituents in **B** and **D** (referred to as Ar^1 and Ar^2, respectively, in the following) compared to **C** may destabilize the *endo*-oxazolidine because of unfavorable steric repulsions. Owing to the similar sizes of Ar^1 [=3,5-$(CH_3)_2C_6H_3$] and Ar^2 [=3,5-$(CF_3)_2C_6H_3$], this effect should be comparable for catalysts **B** and **D**. On the other hand, the electronic contributions of the electron-donating CH_3 and the electron-withdrawing CF_3 groups in **B** and **D**, respectively, should be the inverse and should also have an opposite effect on the enamine amounts with respect to **C** as the reference catalyst. These electronic influences may impact on the enamine stability either by influencing the enamine π system or by changing the H-bond donor ability of the hydroxylic group of the enamine that has been suggested to be essentially involved in the enamine stabilization (see the solvent dependence of prolinol enamines above and our previous study on proline enamines[27]). However, such influences should be observable straightforwardly with the help of ^{1}H NMR chemical shifts as sensors for local electron densities.

The results of the 1D ^{1}H reaction monitoring in DMSO-d_6 as well as the relevant chemical shifts of the enamines formed from **1** and **2** with diarylprolinols **B**−**D** are summarized in Figure 2. Enamine species were detected transiently or permanently in all samples investigated. Concerning the enamine ^{1}H chemical shifts, one distinct trend becomes obvious: From **B** via **C** to **D**, i.e., with stronger electron-withdrawing properties of the aryl rings, downfield shifts of the protons OH (from 4.87/4.88 ppm to 6.37/6.39 ppm with aldehydes **1**/**2**), Hα (from 4.31/4.33 ppm to 4.79/4.77 ppm with **1**/**2**), and also of H2 (from 3.89/3.81 ppm to 3.93/3.88 ppm with **1**/**2**) are observed. On the other hand, the low influence of the catalyst substituents on the chemical shift of H1 indicates that all diaryl prolinol enamines adopt basically the same conformation around the exocyclic C−C bond.[34] In all cases, the enamines were predominantly converted into the *endo*-oxazolidines and again the *exo*-oxazolidines were not observed at all (see Figure S1 in the Supporting Information). However, the degree and the rate of this conversion are largely dependent on the nature of the aryl substituents. For the dimethyl-substituted catalyst **B**, the formation of the *endo*-oxazolidine from the enamines with both aldehydes is similarly fast as for diphenylprolinol (**C**), but the amounts of the enamines of **B** are significantly higher than for **C**: With propionaldehyde (**2**), the enamine **B-2** can be detected for about 3 h in solution, while for 3-methylbutyraldehyde (**1**), the enamine **B-1** does not disappear during more than 12 h but rather coexists with the *endo*-oxazolidine in a constant ratio of 0.6:99.4 (after an induction period). On the other hand, the concentrations of the enamines **D-1** and **D-2**, derived from the trifluoromethyl-substituted catalyst **D**, decrease remarkably more slowly than the ones of **C-1** and **C-2**. In addition, **D-1** and **D-2** are detected easily throughout the observation time of more than 6 h (**D-1** was observed even after more than 3 days) and show constant ratios with the oxazolidines of 3.6:96.4 in the case of **D-1** (after an induction period) and of 2:98 (asymptotically decreasing to this value) in the case of **D-2**. In the case of **D-2**, not only the conversion of the enamine into the oxazolidine is significantly decelerated but also the formation of the enamine itself. This may be rationalized by the detection of an additional intermediate species that was tentatively identified on the basis of its ^{1}H chemical shifts as a carbinolamine of **D** and **2** (Figure 2B; to our knowledge, the detection of a prolinol-derived carbinolamine has not been reported before; see Chart S3A in the Supporting Information for the ^{1}H chemical shift assignment).

For the rationalization of the different enamine amounts observed with the different catalysts **B**−**D**, steric and electronic effects of the phenyl substituents must be taken into account. The common observation of higher enamine amounts with both aldehydes for the CH_3- and CF_3-substituted catalysts **B** and **D** than for the unsubstituted **C** indicates the common increase of the steric bulk as one of the contributions to the relative enamine stabilization. This may be caused by the increased steric repulsion and the associated destabilization of the isomeric *endo*-oxazolidine. The yet increased enamine amounts with catalyst **D** in comparison to **B** furthermore suggest that the enamine

Scheme 1. Performance of Diarylprolinol Organocatalysts B−D in a Direct Crossed-Aldol Reaction of Acetaldehyde According to Hayashi et al.[23] and Comparison of the Reported Yields with the Time Windows in Which the NMR-Detected Amounts of the Enamines B-1, C-1, and D-1 in DMSO-d_6 in Our Study Exceed 1%



π system is stabilized by electron-withdrawing *N*-substituents. The impact of electronegativity changes of the pyrrolidine α-substituent on the enamine π-system is also evidenced by the slight downfield shift of the proton H2 from catalyst **B** to **D**. This relative enamine stabilization in **D-1** and **D-2** is in line with the long-standing observation that enamine−imine tautomeric equilibria are shifted toward the enamine by electron-accepting *N*-substituents and that this effect is most pronounced in polar solvents.[53] In addition, one may speculate that the higher OH acidity of enamines derived from **D** than from **B** or **C**, as evidenced by the downfield-shift of the OH resonance, is accompanied by a higher H-bond donor ability. This may lead to a stronger intramolecular H-bond to the enamine nitrogen[34] and to more favorable interactions with dipolar aprotic solvents such as DMSO and thereby cause an additional relative stabilization of the enamine species. The explanation of the influence of the aldehyde substitution pattern on the enamine amounts is in parallel to our previous study on proline enamines:[27] The higher enamine amounts for **1** than for **2** can be accounted for by the stronger stabilizing +I− and hyperconjugation effects in the enamine and by the stronger steric destabilization of the *endo*-oxazolidine by the isopropyl group in **1**.

In contrast to the amounts of enamines, the different rates of their formation and formal cyclization to the oxazolidines depending on the catalyst structure cannot be explained as straightforwardly at this stage of our investigations. Hence, we cannot yet give a conclusive rationale why the formation of the oxazolidine is so much faster for 3-methylbutyraldehyde (**1**) than for propionaldehyde (**2**). Likewise, the origin of the stabilization of the carbinolamine by catalyst **D** and the reason for the only slow establishment of the enamine−oxazolidine equilibrium in the case of **D** will be addressed in a separate, more comprehensive study on this issue. However, on the basis of the amounts and lifetimes of the enamines observed for the different diarylprolinol catalysts **B**−**D**, i.e., with the help of their "parasitic equilibria" with the isomeric oxazolidines, we can now explain the better conversions in prolinol enamine-catalyzed reactions by **D** than by

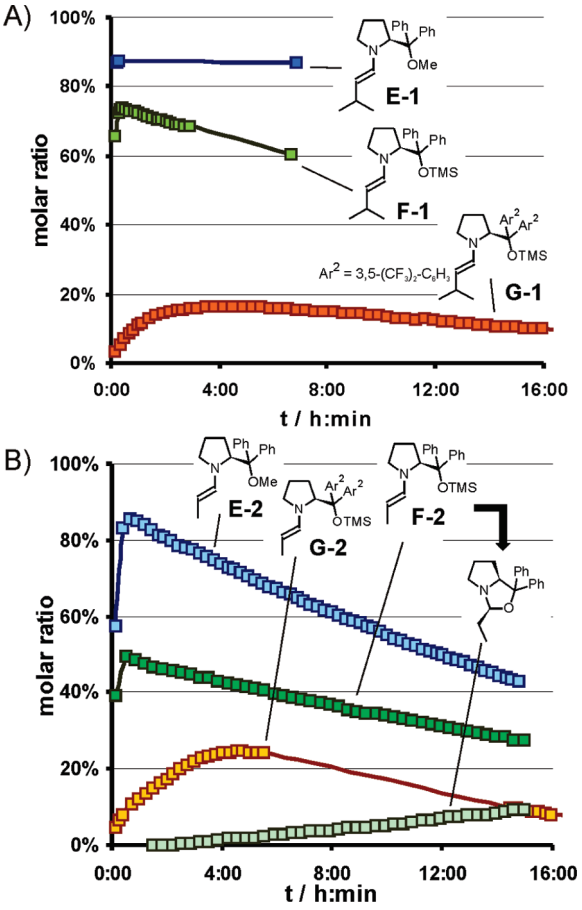


Figure 3. Evolution of the amounts of enamines derived from 3-methylbutyraldehyde (**1**) (A) and propanal (**2**) (B) and the prolinol ether-type organocatalysts **E**−**G** in DMSO-d_6 over time as monitored by 1D ^{1}H NMR spectroscopy. Also shown is the increase of the *endo*-oxazolidine concentration formed from **F-2** upon desilylation (B). (Note: The total amount of aldehyde-derived species in the first spectrum was set to 100%.).

B or **C** as well as the required long reaction times[23,24] on an experimental basis. Accordingly, prolinol enamine catalysis appears to be only successful in the case of sufficient enamine equilibrium concentrations over a reasonably long period of time, as is illustrated most impressively by the results of the Hayashi group on the prolinol enamine-catalyzed crossed-aldol reaction of acetaldehyde (Scheme 1).[23]

Prolinol Ether Enamines. By analogy with the study on prolinol enamines and in order to reveal trends concerning formation, stability, and degradation of organocatalytically more relevant enamines, we investigated mixtures of **1** with the diarylprolinol ether organocatalysts **E**−**G**[8,17,18] in different solvents. This choice was due to the fact that such *O*-protected diarylprolinol derivatives are more broadly applicable and more successfully used for enamine catalysis, particularly as they cannot fall victim to parasitic deactivation by oxazolidine ring closure. Accordingly, enamines of **E**−**G** were readily formed (in situ yields in DMSO-d_6 between 70%[54] and 90% for catalysts **E** and **F**, cf. less than 30% for **A**−**D**) and, in contrast to the enamines of **A**−**D**, they were easily detected even in solvents other than the dipolar aprotic DMSO (see Chart S2 in the Supporting Information). For the example of **E-2**, which had

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shown the highest enamine quantities, a rapid screening for the solvent dependence of the enamine amount was performed. While **E-2** accounted for 85% of the propanal (**2**)-derived species after 0.5 h in DMSO-d_6, this ratio was only 30% in PhMe-d_8, 22% in MeCN-d_3, 16% in $CDCl_3$, and 15% in MeOH-d_4.[55] Hence, just like for prolinol enamines, DMSO provides the best conditions for the stabilization of prolinol ether enamines, too. Most of the experiments mentioned hereafter were therefore performed in DMSO-d_6 as the solvent. The time-dependent evolution of the enamine amounts in the reaction mixtures of aldehydes and prolinol ether catalysts in DMSO-d_6 is depicted in Figure 3.

Two trends are clearly visible therein: First, the absolute amount of enamine decreases depending on the catalyst structure from **E** over **F** to **G**. While the equilibrium between the enamine (and water) and the starting materials **1**, **2**, and **E**−**G** is shifted almost completely toward the enamine in the case of the diphenylprolinol methyl ether **7**, the sterically more demanding TMS (trimethylsilyl) moiety of **F** causes lower amounts of the enamine and substitution of the phenyl ring by the even bulkier Ar^2 in **G** further reduces the concentration of the enamine significantly.[56] From a thermodynamical point of view, this reveals that the relative stability of the enamine with respect to the starting material decreases with increasing bulkiness of the α-substituent of the pyrrolidine ring. This in turn indicates that the effective shielding of one face of the enamine by the bulky α-substituent, desired for high stereoselectivities of the catalyst, comes along with unfavorable steric interactions between the "obese" substituent and the aldehyde alkyl chain that lead to a certainly undesired reduction of the active enamine intermediate concentration. The fact that this trend is brought about by enlarging the *O*-protecting group as well as the meta-substituents on the phenyl ring is in line with the finding from our conformational investigations on such enamines that both of these groups interact with the enamine moiety and play a role in the stereoselection in enamine catalysis by prolinol (ether) derivatives.[34]

Second, the nature of the *O*-protecting group and the phenyl meta-substituents of the catalysts **E**−**G** also have an impact on the formation rate and the persistence of the corresponding enamines. The enamine **E-1** is formed within minutes in DMSO-d_6 and proved to be stable over the period of time observed. The enamines **E-2**, **F-1**, and **F-2** appear rapidly, too; however, their amounts decrease over time. In the case of **E-2**, this is due to the consumption of the enamine by unproductive reactions, but not due to the demethylation of the catalyst moiety. In contrast, for **F-1** and **F-2** and likewise for **G-1** and **G-2**, the loss of the TMS-protecting group is observed and the subsequent cyclization to the oxazolidine (see above) is mainly responsible for the decrease of the enamine concentration.[57] This cleavage of the silyl ether has already been alluded to in the literature[30,58,59] but is monitored here experimentally for the first time (Figure 3B). Hence, according to our findings in DMSO-d_6, the replacement of TMS by Me to increase the stability of the catalyst against cleavage of the *O*-protecting group and hence to facilitate, for instance, mechanistic investigations[60] seems well justified.

In addition, by comparison with **F-1** and **F-2**, the formation rates of the enamines **G-1** and **G-2** in DMSO-d_6 are drastically reduced so that their maximum concentrations are reached only after more than 4 h. Certainly, a reduced rate of enamine formation might be a critical point for the application of prolinol ether-type organocatalysts in enamine catalysis. To understand and to avoid this potentially detrimental effect, we searched for

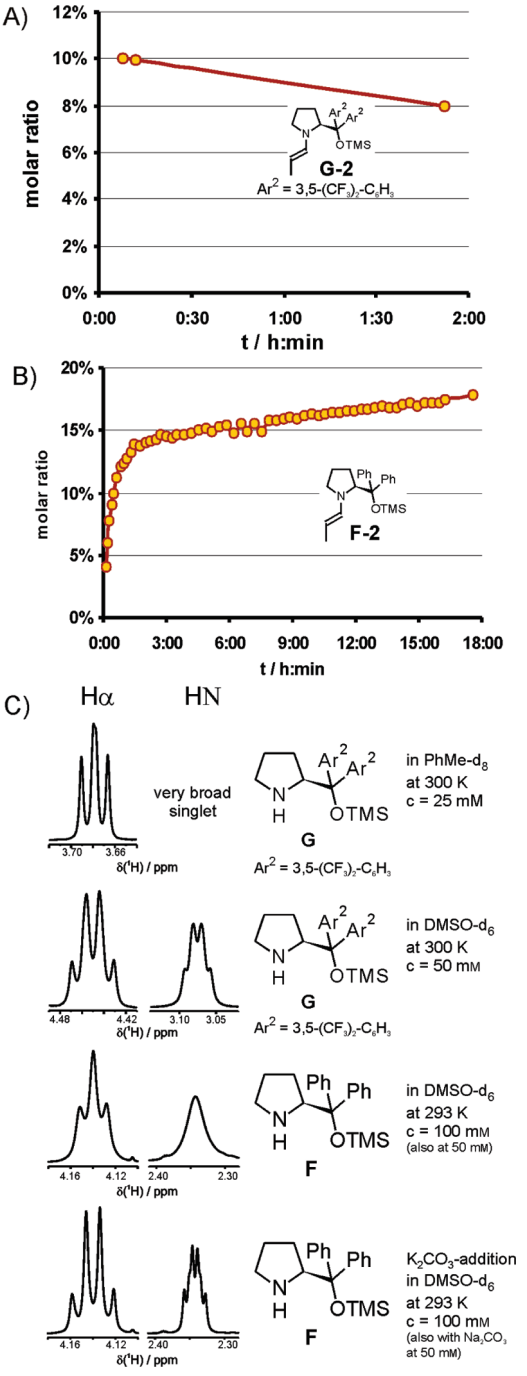

Figure 4. Evolution of the amounts of enamine derived (A) from propanal (**2**) and the diarylprolinol ether **G** in PhMe-d_8 and (B) from **2** and the diphenylprolinol ether **F** with 100 mol % K_2CO_3 in DMSO-d_6 over time as monitored by 1D ^{1}H NMR spectroscopy. (Note: The total amount of aldehyde-derived species in the first spectrum was set to 100%.) (C) ^{1}H NMR resonances of Hα (left column) and HN (right column) of **G** in PhMe-d_8 (first row), of **G** in DMSO-d_6 (second row), of **F** in DMSO-d_6 (third row), and of **F** in DMSO-d_6 with 100 mol % of K_2CO_3 (fourth row): Additional resonance splittings of the signals for **G** and **F**/K_2CO_3 in DMSO-d_6 are indicative of the presence of $^3J_{H,H}$ couplings to HN.

different experimental conditions (solvent, basic additives,[61] etc.) that either promote or prevent the delayed enamine formation: Interestingly, the enamine formation is not slowed

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down in DMSO-d_6 when the substituents Ar^2 of **G** are replaced by Ph (see **F-1** and **F-2** in Figure 3). Likewise, the delayed enamine buildup is not observed for **G** and **2** if the solvent is changed from DMSO-d_6 to PhMe-d_8 (see Figure 4A). On the other hand, the enamine formation *is* decelerated when **F** is used in DMSO-d_6 together with K_2CO_3 as an additive (see Figure 4B). These observations lead us to the conclusion that unfortunate combinations of catalysts, additives, and solvents (with regard to Figure 2 also of aldehydes) can cause delayed enamine formations in solution. Interestingly, distinct experimental observations and parameters are connected to the decelerated enamine formation: On the one hand, in the case of the prolinol enamine **D-2**, a carbinolamine as a further intermediate on the way to the enamine seems to be stabilized, which can delay the enamine formation (see Figure 2B). A similar species, possibly the prolinol ether **F**-derived analog, was observed in the case of **F**/K_2CO_3 as the catalytic system in DMSO (data not shown). On the other hand, a deceleration of the NH proton exchange was observed for prolinol ethers (see below). This may be caused by steric crowding in proximity to the pyrrolidine nitrogen atom and solvent and/or additive molecules that are H-bonded to the NH proton. Such an effective shielding of the nitrogen of the prolinol ether catalyst may hamper the enamine formation with the aldehyde: In the case of the sterically crowded catalyst **G**, DMSO as the solvent may be assumed to block the nitrogen, whereas in the case of the less crowded **F** an additional small and multiple H-bond acceptor such as the carboxylate ion can exert this effect.

If this hypothesis is true, one should be able to prove the steric shielding of the nitrogen atom experimentally by a reduced exchange rate of the nitrogen-bound proton H^N. For instance, such reduced exchange rates can be evidenced NMR spectroscopically by the observation of homonuclear scalar couplings to the exchangeable proton or by identical diffusion coefficients of exchangeable and nonexchangeable protons within the same molecule. Indeed, both of these NMR spectroscopic features were observed on the level of catalyst/additive solvent combinations only in those cases, for which decelerated enamine formation was observed, too, i.e. for **G** in DMSO-d_6 and for **F**/K_2CO_3 (likewise for **F**/Na_2CO_3) in DMSO-d_6, but most notably not for **F** with other basic additives such as acetates (NaOAc, KOAc) or NEt_3. First, the hampered H^N exchange manifests itself in the appearance of scalar proton−proton couplings $^3J_{H,H}$ between H^N and the adjacent protons Hα and Hδ1,2 in the one-dimensional ^1H spectra (see Figure 4C). Second, the slow H^N exchange is also evidenced from DOSY investigations (data not shown): For **F**/K_2CO_3 in DMSO-d_6, identical diffusion coefficients are observed for H^N and the nonexchangeable protons of the catalyst **F**. In contrast, in the absence of K_2CO_3 the diffusion of H^N appears to be a lot faster than the one of the nonexchangeable protons of **F** because of the exchange of H^N with the faster diffusing residual water in the sample during the diffusion period of 50 ms. Both the $^3J_{H,H}$ scalar couplings to H^N and the diffusion coefficients of H^N indicate a substantially slower exchange of the nitrogen-bound proton H^N for **G** or **F**/K_2CO_3 in DMSO than in all the other cases and are therefore in line with our hypothesis of a combination of steric crowding and H-bonding interactions at the nitrogen atom that compromises the tendency of the nitrogen to form enamines.

These two NMR spectroscopic characteristics may hence be regarded as a very simple and rapid method to check catalyst/additive solvent combinations for the delayed enamine formation with aldehydes (see Figure 5 for a graphical summary of this screening method and Charts S4 and S5 in the Supporting Information for the NMR assignments of the catalysts). This may help to avoid the resulting, potentially disadvantageous effects in diarylprolinol silyl ether catalysis; for instance, one may speculate that the delayed enamine formation is one of the reasons for the inferior performance of **G** in DMSO than in other solvents[62] and for the even more detrimental effect of K_2CO_3 than of other basic additives (NaOAc and NEt_3) to **F** in DMSO.[63]

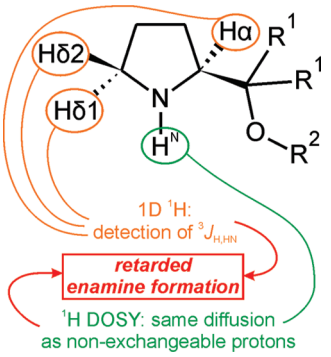

Figure 5. Graphical summary of the screening methods for the decelerated formation of prolinol (ether) enamines on the early level of the catalyst/additive solvent combination.

CONCLUSION

In summary, we have investigated the formation and stability of enamines derived from prolinol (ether)-type organocatalysts with two different aldehydes in various solvents by means of NMR spectroscopy. For all enamines studied, the *E*-configuration is adopted predominantly. For prolinol ether enamines with small aldehyde alkyl chains, we could evidence for the first time the presence of the *Z*-isomer besides the *E*-enamine in solution.

For prolinol-derived catalysts, the first in situ detection of enamine intermediates is presented. Similarly to proline enamines, they can be observed only in the dipolar aprotic solvent DMSO, but not in methanol, acetonitrile, chloroform, or toluene. In contrast to proline, however, these prolinol enamines are shown to coexist in a "parasitic equilibrium" with the isomeric oxazolidines, since they rapidly undergo cyclization. In the case of prolinol, the oxazolidine formation is easily reversible and the thermodynamic equilibrium between the enamine and both oxazolidines is slowly established. For diphenylprolinol, the geminal phenyl rings shift this equilibrium, presumably through the Thorpe−Ingold effect, virtually completely toward the exclusively detected *endo*-oxazolidine, which is then appropriately termed a "dead end" of prolinol enamine catalysis. Yet, this state can be overcome by destabilizing the *endo*-oxazolidine and by stabilizing the prolinol enamine with the help of bulkier and electron-withdrawing aryl substituents. In this context, also the first prolinol-derived carbinolamine was detected in situ.

Diarylprolinol ether enamines are detected readily in situ. Their amounts decrease with increasing sizes of the aryl rings and of the *O*-protecting group, probably owing to steric conflicts with the enamine moiety. Methyl ether enamines are more robust than silyl ethers as, for the latter, we could monitor the desilylation and subsequent cyclization to the oxazolidine in DMSO. A drastically delayed formation of the prolinol ether enamines is

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observed for unfortunate combinations of aldehydes, catalysts, solvents, and additives, possibly caused by the stabilization of carbinolamines and/or by the steric shielding of the nitrogen atom. Based on its concordance with a reduced exchange rate of the nitrogen protons, a rapid and facile 1D ^{1}H- or DOSY-based screening method on the level of the catalytic systems themselves is presented for this potentially detrimental effect.

On the basis of the examples of prolinol- and prolinol ether-derived enamines, we illustrate the impact of both the size and the electronic properties of the pyrrolidine substituent on the delicate interplay between intermediate selectivities and reactivities in terms of the conformational preferences (s-cis/*s*-trans) of enamines, their amounts, and their robustness. Our results hence provide a broad experimental basis for an improved understanding of enamine catalysis by diarylprolinol (ether)s. They should also inspire further studies on the elucidation of the prolinol (ether) enamine formation pathway, including the role of oxazolidines and carbinolamines therein and the issue of the enamine formation rate. Likewise, they are expected to pave the way for conformational investigations aiming at the origin of stereoselection exerted by prolinol (ether) organocatalysts. From a more practical point of view, helpful advice for the optimization of reaction conditions is provided for synthetically working organic chemists. Despite their tremendous success in enamine catalysis, there is still sufficient space for improving the scaffolds of prolinol ether organocatalysts, for instance, by avoiding *O*-deprotection in solution or too long reaction times, caused by low enamine amounts and formation rates. In this context, our rapid screening method may facilitate the future optimization of the prolinol (ether) catalyst scaffold by substituent variations. On this basis, also the fine-tuning of the selectivity−reactivity balance for prolinol catalysts ("parasitic equilibrium") should be facilitated and might help to expand the scope of prolinol derivatives for enamine catalysis.

EXPERIMENTAL SECTION

Enamines were created in situ inside a standard 5 mm NMR tube by adding freshly distilled aldehydes **1** or **2** (30 μmol, if not stated otherwise) to a solution of 1 equiv of the organocatalysts **A**−**G**, respectively, in 0.6 mL of deuterated solvent. The NMR tube was transferred to the spectrometer immediately after the mixing of all reacting components.

NMR measurements were performed at 300 K on a Bruker Avance DRX 600 (600.13 MHz) and on a Bruker Avance III 600 (600.25 MHz) spectrometer, the latter equipped with a TCI cryoprobe with *z*-gradient (53.5 G/cm). Reaction monitoring by 1D ^{1}H NMR spectra was employed to identify appropriate time slots for more detailed 2D NMR spectroscopic investigations: ^{1}H,^{1}H-COSY, ^{1}H,^{1}H-NOESY/EXSY (mixing time 700 ms), ^{1}H,^{13}C-HSQC, and ^{1}H,^{13}C-HMBC spectra were recorded for the characterization of the observed species if information from 1D NMR spectra proved to be insufficient. NMR data were processed and evaluated with Brukeŕs TOPSPIN 2.1.

ASSOCIATED CONTENT

Supporting Information. NMR spectroscopic characterization of organocatalysts, enamines, and a carbinolamine as well as the NMR monitoring of oxazolidine formation. This material is available free of charge via the Internet at http://pubs.acs.org.

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(55) In MeOH-d_4, about 80% of the initial amount of **2** was found by 1D ^{1}H spectra in a species that must be assigned as either the hemiaminal of **2**, **E**, and water or the hemiaminal ether of **2**, **E**, and methanol.
(56) Interestingly, the steric destabilization of the prolinol ether enamine by Ar^2 thereby seems to exceed the electron-withdrawing stabilization by Ar^2 that was observed for prolinol enamines. This can be explained in the context of the different enamine conformations of prolinols and prolinol ethers observed in our parallel enamine conformation study. Note: These differences in the amounts of enamines cannot be accounted for by different amounts of residual water within the samples, since the 1D ^{1}H NMR integration indicates that the amount of water was the highest in the sample with **E** and the lowest in the sample with **G**.
(57) Interestingly, the desilylation of prolinol silyl ethers seems to be most critical in DMSO. The results of more detailed studies on this issue will be reported in due course.
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(61) While prolinol ether catalysts are commonly used together with acids as additives in iminium catalysis, basic additives (NEt_3, NaOAc, K_2CO_3, lutidine, etc.) are also employed together with catalyst **F**, such as for alkylations or related domino reactions. For selected representative examples, please see the following: (a) Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450–451. (b) Fu, A.; List, B.; Thiel, W. *J. Org. Chem.* **2006**, *71*, 320–326. (c) Xie, H.; Zu, L.; Li, H.; Wang, J.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 10886–10894. (d) Wang, J.; Li, H.; Xiw, H.; Zu, L.; Shen, X.; Wang, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 9050–9053. (e) Ibrahem, I; Zhao, G.-L.; Rios, R.; Vesely, J.; Sundén, H.; Dziedzic, P.; Córdova, A. *Chem.—Eur. J.* **2008**, *14*, 7867–7879. (f) Also, see ref 63.
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