Distinct conformational preferences of prolinol and prolinol ether enamines in solution revealed by NMR†

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Enamines, which are key intermediates in organocatalysis derived from aldehydes and prolinol or Jørgensen–Hayashi-type prolinol ether catalysts, were investigated conformationally in different solvents by means of NMR spectroscopy, in order to provide an experimental basis for a better understanding of the origin of stereoselection. For all of the enamines studied, surprisingly strong conformational preferences were observed. The enamines of the diarylprolinol (ether) catalysts were found to exclusively exist in the s-trans conformation due to the bulkiness of the pyrrolidine α-substituent. For prolinol enamines, however, a partial population of the s-cis conformation in solution was also evidenced for the first time. In addition, for all of the enamines studied, the pyrrolidine ring was found to adopt the down conformation. Concerning the exocyclic C–C bond, the sc-exo conformation, stabilized by CH/π interactions, is exclusively observed in the case of diarylprolinol ether enamines. In contrast, diarylprolinol enamines adopt the sc-endo conformation, allowing for an OH...N hydrogen bond and a CH/π interaction. A rapid screening approach for the different conformational enamine features is presented and this was applied to show their generality for various catalysts, aldehydes and solvents. Thus, by unexpectedly revealing the pronounced conformational preferences of prolinol and prolinol ether enamines in solution, our study provides the first experimental basis for discussing the previously controversial issues of s-cis/s-trans and sc-endo/sc-exo conformations. Moreover, our findings are in striking agreement with the experimental results from synthetic organic chemistry. They are therefore expected to also have a significant impact on future theoretical calculations and synthetic optimization of asymmetric prolinol (ether) enamine catalysis.

Introduction

In-depth studies on intermediate species are highly important for a better understanding of the mechanistic principles that underlie organic reactions. In particular, in the important and ever growing field of stereoselective catalysis, conformational analyses of active intermediates may guide researchers towards the origin of stereocentro in asymmetric reactions and are, therefore, highly valuable for the directed optimization of already existing catalysts and the design of novel high-performance catalysts. Modern asymmetric organocatalysis,1–5 with its manifold different concepts and activation modes,6,7 such as non-covalent catalysis via phase transfer,8 or hydrogen bonding,9–11 or Brønsted acids12,13 as well as covalent catalysis via Lewis bases,14 has substantially contributed to the field of stereoselective catalysis during the last few years. Typically by making use of compounds originating from the chiral pool, catalysis by secondary amines15–17 through enamine,18,19 iminium,20,21 or SOMO22–24 activation has emerged as one of the most successful and widely applicable principles. In particular, proline25–27 and Jørgensen–Hayashi-type prolinol ethers28–33 have been proven to give remarkable performances in asymmetric iminium and enamine organocatalysis. Also, prolinol organocatalysts34 have found a use based on enamine intermediates35–38 although they are mainly employed in iminium catalysis.

However, regarding the vast number of synthetic applications, conformational studies on enamine intermediates, especially on the origin of their stereoselection, are rather scarce and experimental investigations in solution are completely nonexistent so far. This can be partially ascribed to the currently limited number of reports on relevant enamines in solution; no more than two prolinol silyl ether-type enamines have been observed in situ. Therefore, the conformations of such enamine intermediates in solution are largely unknown and conformational information

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has, so far, been limited to theoretical calculations and crystal structure analyses. However, these approaches may be affected by vacuum calculation artifacts or crystal packing effects. Accordingly, conflicting results concerning the conformational preferences of both the exocyclic N–C bond and the exocyclic C–C bond of diarylprolinol ether enamines have been reported from these studies. Therefore, experimental results in solution are highly desirable to clarify these issues. Only recently have we expanded the available pool of enamines in solution by the first enamine intermediates derived from proline and prolinols and by various aldehyde-derived prolinol ether enamines. Thus, the experimental basis is available for more detailed conformational studies on enamine intermediates in solution. This should help to clarify the origin of stereoselection and, hence, to tailor optimized organocatalysts.

In this article, we present the first detailed in situ investigations on the conformations of aldehyde-derived prolinol and prolinol ether enamines in different solvents by means of NMR spectroscopy. 1H,1H-NOESY spectra reveal the preference of the enamine s-trans arrangement due to the steric influence of the pyrrolidine a-substituent. In addition, the pyrrolidine ring was shown by scalar coupling constants to predominantly adopt the down conformation, which allows for intramolecular CH/π interactions between pyrrolidine protons and the aryl groups of the “obese” a-substituent. In the case of diarylprolinol ether enamines, the sc-exo conformation for the exocyclic Cα-Cε bond was exclusively observed, which is stabilized by two CH/π interactions. In contrast, for the diarylprolinol-derived enamines, only the sc-endo conformation was found, which allows for both an OH···N hydrogen bond and one CH/π interaction. In addition, we present a rapid and facile 1D 1H NMR-based screening approach for this conformational feature that plays a key role in the shielding of one face of the enamine and, hence, in the stereocontrol effectuated by the organocatalyst.

Results and discussion

Model enamines

On the basis of our recent studies on proline enamines and on the formation and stability of prolinol (ether) enamines in solution, various typical secondary amine organocatalysts (Scheme 1: 1–7) were selected for our conformational enamine study. Two different aliphatic aldehydes with alkyl chains of different sizes, 3-methyl-butyraldehyde a and propionaldehyde b (Scheme 1), were chosen with regard to the suppression of the self-aldolization (a) and to a substantial relevance for synthetic applications (b). To allow for the comparison of prolinol and prolinol ether enamines, we predominantly used DMSO in our conformational investigations, since it is the only solvent in which prolinol enamines have been detected so far. For prolinol ether enamines, further solvents (methanol, acetonitrile, chloroform, dichloromethane, and toluene) were then used to explore the generality of the conformational preferences.

All of the experiments were conducted in NMR tubes by mixing equimolar amounts of the aldehyde and catalyst in deuterated solvents in order to obtain concentrations of 50 mmol L⁻¹ each and NMR spectra were recorded at 300 K (see the supplementary information for details†). Overall, 14 different enamines were formed from the aldehydes a–b and the organocatalysts 1–7 (designated as “catalyst-number.aldehyde-character”, i.e. 1a–7b in Scheme 2) were obtained in situ and investigated in different solvents. The detection and characterization as mainly E-configured enamines has been reported recently.† (See also Schemes S1 and S2 in the supplementary information for the NMR assignments†.)

Enamine conformations

Besides the already reported aspects concerning the stability, formation and degradation of enamine intermediates, knowledge on how the stereoselectivity is controlled in the bond-forming step is of utmost importance for the understanding of asymmetric organocatalyzed reactions. On the basis of previous theoretical calculations and crystal structure analyses, and in agreement with previous experimental results, it is generally assumed that the methanol(ether)-substituent of the

Scheme 1 A) Aldehydes and organocatalysts studied. B) Atom nomenclature used for the respective enamines.

Scheme 2 The investigated E-enamines derived from aldehydes a and b and catalysts 1–7, displayed in the favorable s-trans conformation.
pyrroldine ring secures both the *s-trans* arrangement of the enamine and the effective shielding of one face of the enamine π system, thereby directing incoming electrophiles to the opposite side.\(^\text{396}\) In the following paper, we present the results of our conformational investigations of the prolinol (ether) E-enamines 1a–7b in solution by NMR spectroscopy, mainly by ¹H,¹H-NOESY spectra. Addressing the conformational preferences of the pyrroldine ring and of the exocyclic N–C1 and Cα–Cδ bonds (see Scheme 1B for the atom nomenclature), we provide the first detailed insights into the three-dimensional solution structures of these reactive intermediates in organocatalysis.

### s-cis and s-trans: Conformation of the exocyclic N–C1 bond

Shifting the equilibrium between the two enamine conformations s-cis and s-trans (with respect to the N–C1 single bond with partial double bond character, Fig. 1A) towards the s-trans conformation, most likely by steric repulsion, is one of the two proposed functions of the (diaryl)methanol (ether) substituent in the α-position of organocatalysts 1–7.\(^\text{396}\) In analogy to the relative s-cis and s-trans enamine stabilities, a preference of the corresponding isomeric E-iminium ion over the Z-isomer can be assumed, as both biases are thought to originate from the same steric effect (Fig. 1A).\(^\text{396}\) The guarantee of this basic conformational feature of the enamine key intermediate by the bulky α-subsituent is believed to be essential for the stereochemical outcome of prolinol(ether)-catalyzed reactions. For instance, we have recently pointed out the stereochemical implication of the s-cis s-trans enamine equilibrium for the formation of the isomeric cyclic oxazolidines by prolinol catalysts.\(^\text{46}\) The predominance of the s-trans conformation in the case of proline enamines has been proposed from calculations\(^\text{48}\) and has been experimentally proven by our NMR studies in solution;\(^\text{47}\) in addition, exclusively s-trans proline enamines have been detected in crystal structures.\(^\text{49}\) Likewise for prolinol ether enamines, the s-trans conformation has been observed in crystal structures\(^\text{49}\) and its energetic preference has been thoroughly calculated.\(^\text{39,41,43–45}\) Interestingly, the generally accepted assumption that s-trans enamines of diarylprolinol silyl ethers are a lot more stable than the s-cis enamines has recently been challenged by a theoretical study that predicted similar energies and, hence, similar populations of both conformations using gas-phase calculations.\(^\text{44}\)

To experimentally clarify this issue in solution, we analyzed the ¹H,¹H-NOESY spectra of enamines 1b–7b (example sections are shown in Fig. 1B). The relative intensities of the NOEs between H1 and the protons Hz or Hδ1,2 are considered to be a suitable indicator for the differentiation between the s-trans and the s-cis conformations (Fig. 1A). For the s-trans conformation, a stronger NOE between H1 and Hz is expected, while a stronger NOE between H1 and Hδ1,2 would be indicative of a predominant population of the s-cis conformation. The ¹H,¹³C-HMBC cross-peak intensities between H1 and Cα or Cδ can be used as an additional criterion, since ²JHC couplings are known to be larger in an antiperiplanar than in a synperiplanar arrangement.\(^\text{40}\) Accordingly, a larger HMBC cross-peak H1–Cδ is indicative of the s-trans conformation, whereas the s-cis conformation would be revealed by a larger H1–Cα cross-peak. In our NOESY experiments, significantly more intensive cross-peaks from H1 to Hz than to Hδ1,2 were observed for all of the enamines investigated, *i.e.* for 1b, 3a-b, 5a-b, 6a-b and 7b in DMSO-\(d_{6}\), for 5b in CDCl\(_3\) and for 7b in PhMe-\(d_{8}\). This indicates that the s-trans conformation is indeed preferably populated by enamines derived from α-substituted pyrroldines and different aldehydes in both polar and non-polar solutions. This finding was confirmed by the ¹H,¹³C-HMBC spectrum of enamine 6b. The more intensive cross-peak between H1 and Cδ in comparison to H1 and Cα (Fig. 1B, right) indicates a larger ²JHC coupling between H1 and Cδ and, thus, also reveals the preferred adoption of the s-trans conformation.

Furthermore, using quantitative NOESY analyses we studied to what extent the methanol (ether) substituent impacts on the actual position of the s-cis s-trans equilibrium (Table 1). For this purpose, the volume of the NOESY cross-peak between H1 and Hz was compared to the sum of the cross-peak volumes between H1 and Hδ1,2. The larger the ratio NOE(H1–Hδ1,2):NOE(H1–Hδ1,2), the larger the contribution of the s-trans conformation to the s-cis s-trans equilibrium is in solution. The theoretical ratio NOE(H1–Hz):NOE(H1–Hδ1,2) for a pure s-trans enamine was

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**Fig. 1** A) Left: atom nomenclature; right: the equilibrium between the enamine conformations, their relation to iminium ions and the distinctive NOEs and ²JCH. B) Sections of the ¹H,¹H-NOESY spectra of 1b (left) and 5b (middle) and of a ¹H,¹³C-HMBC spectrum of 6b (right) in DMSO-\(d_{6}\) at 300 K.

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Table 1  Experimental NOESY cross-peak volumes for the various enamines and theoretical values based on the calculated s-trans enamine structures

<table>
<thead>
<tr>
<th>NOE pair</th>
<th>1b</th>
<th>5b, 6b, 7b</th>
<th>5a, 6a</th>
<th>Theoretical values (s-trans enamines)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>H</em></td>
<td><em>Ar</em></td>
<td><em>Ph</em></td>
<td><em>H</em></td>
</tr>
<tr>
<td></td>
<td><em>Me</em></td>
<td><em>Me/TMS</em></td>
<td><em>Me/TMS</em></td>
<td></td>
</tr>
<tr>
<td>H1-Hz</td>
<td>≤79°</td>
<td>91-94</td>
<td>90-91</td>
<td></td>
</tr>
<tr>
<td>H1–H31 + H1–H52</td>
<td>≥21°</td>
<td>6–9</td>
<td>9–10</td>
<td>12</td>
</tr>
</tbody>
</table>

* The short lifetimes of diphenylprolinol enamines 3a and 3b, resulting in poor spectral resolution, did not allow a reliable NOESY integration. b For 1b, the peaks of Hα and one of the protons Hε overlap. Therefore, the ratio of 8 : 2 is an upper limit and the actual increase in the cross-peak ratio from 1b to 5b/6b/7b should be significantly higher.

Calculated on the basis of the internuclear distances from the DFT-optimized s-trans prolinol ether enamine structures provided in the literature. From this calculation, the maximum NOE ratio is about 9 : 1 for the pure s-trans conformation and, accordingly, cannot be exceeded further (Table 1, right).

From the experimental NOESY cross-peak integration of enamine 1b (Table 1), it becomes obvious that the theoretical value for the pure s-trans enamine conformation (about 9 : 1) is not reached for prolinol (1). This indicates the partial adoption of the s-cis conformation by 1b and, hence, represents the first experimental evidence that the s-cis conformation significantly contributes to the conformational ensemble of a prolinol enamine in solution. This interpretation is also supported by the recently reported slow equilibration of the isomeric prolinol oxazolidines, presumably via the s-trans–s-cis isomerization of the enamine. In contrast, the increasing sizes of the pyrrolidine α-substituents in the catalysts 5–7 lead to an increase in the NOESY cross-peak volume ratio NOE(1H1–H3z)NOE(1H1–H51,2), from less than 8 : 2 to more than 9 : 1. This indicates that bulkier α-substituents indeed enforce the strong preference for the s-trans enamine conformation. However, interestingly, there is no additional visible increase in the NOESY cross-peak ratio with further enlargement of the pyrrolidine α-substituent (e.g. from 5b over 6b to 7b) or the aldehyde alkyl chain (compare entries for 5b,6b with 5a,6a). For all of these diarylprolinol ether enamines, the congruence of the experimental NOE ratios of about 9 : 1 with the theoretical values for the pure s-trans conformation suggests that the “saturation” of the NOESY cross-peak ratio and, accordingly, of the corresponding s-cis to s-trans population ratio can be understood in terms of an almost exclusive adoption of the s-trans conformation. In addition, this postulation of a negligible s-cis population of diarylprolinol ether enamines is also in line with our observations on the exclusive formation of the endo-oxazolidines by diarylprolinol catalysts.

Conformation of the pyrrolidine ring: up and down

To the best of our knowledge, no attention has been paid to the potential influence of the puckering of the pyrrolidine ring on the overall conformation of enamines derived from prolinol-based organocatalysts. Only for proline-derivatives has the pyrrolidine conformation in aldol transition states been theoretically studied. This previous lack of interest is striking in view of the fact that the pyrrolidine ring is known to be an important structure, since proline as an organocatalyst has been found to provide significantly better yields and stereoselectivities than related catalysts with four- or six-membered rings. Accordingly, in the context of diarylprolinol ether enamines, only one single comment on the pyrrolidine conformation has become known to us from an X-ray study that states that “the puckering of the pyrrolidine ring varies from structure to structure”. However, to our mind, the conformational preferences of the pyrrolidine ring should be considered in more detail for two reasons. Firstly, pyrrolidine hydrogen atoms may potentially participate in stabilizing CH/π interactions with the phenyl rings in diarylprolinol (ether) enamines; these weak interactions have been proven to have important implications not only in biochemistry, but also in molecular recognition and organic chemistry. Secondly, in general, different pyrrolidine ring conformations may well be associated with different reactivities and the catalytic performances of the respective compounds. In particular, diarylprolinol ether enamines the pyrrolidine up conformation, in combination with the known slight pyramidality of the enamine nitrogen atom, creates a concave surface for the attack of the electrophile (the convex surface is supposed to be shielded by the “obese” α-substituent, Fig. 2A, left), which is known to be a sterically unfavorable situation. In contrast, the down conformation the enamine surface opposite to the “obese” substituent is convex and, hence, is wide-open for the electrophilic attack towards the enamine.
in peptides and the enamine moiety in organocatalytically active intermediates (on the basis of prolinol ether enamine crystal structures\cite{39} and DFT calculations\cite{40,41,42}). In addition, the scalar coupling constant \( J \) criteria for proline side-chain conformations can be applied also to diarylprolinol (ether) enamines, as no systematic shift of the \( J(H_x,H_B) \), potentially caused by the different C\(\beta\)-substituents, is observed for the free catalysts proline and 2–7 (see Schemes S3 and S4 in the supplementary information\cite{†}). The two different pyrrolidine conformations \textit{up} down can be distinguished by NMR via their characteristic \( J_{\text{HH}} \) values, which are easily extracted from well-resolved \( ^1\text{H} \) resonance multiplet patterns. Accordingly, small \( J(H_x,H_B) \) and \( J(H_B2,H_Y1) \) indicate the population of the \textit{down} conformation, while small \( J(H_S1,H_Y2) \) are indicative of the \textit{up} conformation. The two conformations \textit{up} down and the associated theoretical and experimentally observed \( J_{\text{HH}} \) values are summarized in Fig. 2.

For diarylprolinol (ether) enamines 2a–7b, small vicinal couplings of 1.5–2.5 Hz and 2–3 Hz, respectively, were found for \( J(H_x,H_B) \) and \( J(H_B2,H_Y1) \), (not only in DMSO-\textit{d}6, but also in MeCN-\textit{d}3, CDCl3 and PhMe-\textit{d}6, see Scheme S1 in the supplementary information\cite{†}). In contrast, values in the range 6–10 Hz were detected for \( J(H_S1,H_Y2) \), which leads to the characteristic multiplet patterns depicted in Fig. 2C for the example of 6a.

\( \text{(Unfortunately, coupling constants could not be extracted for 1a and 1b due to spectral overlap and higher order NMR signals.)} \)

The experimental values for \( J(H_x,H_B) \) and \( J(H_B2,H_Y1) \) equal those expected for the pure \textit{down} conformation.\cite{66} This indicates the \textit{down} conformation for the pyrrolidine ring in diarylprolinol (ether) enamines in solvents ranging from DMSO over MeCN to CHCl3 and PhMe. In addition, the small \( J(H_x,H_B) \) and \( J(H_B2,H_Y1) \) show that conformations with large coupling constants, e.g. \textit{up}, do not substantially contribute to the conformational ensemble, which can be taken as an indication of a rather stable structure.\cite{67} Interestingly, for the aldol transition states of the proline-derived catalysts, the theoretical calculations suggested that the \textit{down} conformation is significantly preferred only for \( \beta\)-substituted pyrrolidine rings.\cite{51} However, our experimental study reveals a high preference for the \textit{down} conformation, even in the absence of \( \beta\)-substituents. In contrast, in free catalysts 2–7, both \( J(H_x,H_B) \) are larger than 7 Hz, which indicates a dynamic equilibrium of the \textit{up} and \textit{down} conformations (see Schemes S3 and S4 in the exemplary \( ^1\text{H} \)3 multiplets in Fig. 3C of our previous report.\cite{46}).

These experimental results show that the enamine formation is essential for the adoption of a conformational preference of the pyrrolidine ring. This means that the approximate planarity of the enamine moiety, along with the bulky \( \alpha\)-substituent, imposes conformational constraints on the pyrrolidine ring to such a degree that one pyrrolidine conformation (\textit{down}) is exclusively observed. As a first assumption, this may be rationalized by the
different steric repulsion modes within the up and down conformations presented in Fig. 2A. The up conformation may be destabilized by the detrimental repulsion between the “obese” \( \alpha \)-substituent and the vicinal \( \beta \), as well as the \( \delta \) protons, which is reduced in the preferred down conformation (Fig. 2A; this hypothesis parallels the observed slight pyramidalization of the enamine nitrogen known from crystal structure analyses\(^{19} \) and DFT calculations.\(^ {39b,41,43-45,51} \)) Furthermore, for proline derivatives, the down conformation has been calculated to be compatible with less deviation of the enamine moiety from the favorable planarity than the up conformation.\(^ {39a} \) In addition, it is only the down conformation that creates sufficient spatial proximity between the methanol ether substituents and the \( \mathrm{H}_2 \gamma \) of the pyrrolidine ring (Fig. 2A) to potentially allow for stabilizing CH/\( \pi \) interactions (see below). Finally, only in the down conformation, the attack of an electrophile occurs in a sterically favorable manner to the unshielded and convex surface of the enamine.

**Orientation of the diarylmethanol substituent by rotation around the exocyclic \( \mathrm{C}_a–\mathrm{C}_c \) bond: sc-exo, sc-endo and ap**

The effective shielding of one face of the enamine \( \pi \) system, leading to the approach of incoming electrophiles from the opposite side, is meant to be the second important function of the diaryl-methanol (ether) substituent for the stereochemical outcome of enamine-catalyzed reactions by organocatalysts\(^ {2–7,39a} \). However, beyond empirical experience on catalyst performances, very little is known about whether this shielding is brought about by the O-protecting group or the phenyl rings of the “obese” substituents of diarylprolinol(ether)-type organocatalysts. This issue, which is highly important for theoretical calculations aimed at the understanding of the stereoselection, is closely connected to the conformation of the exocyclic \( \mathrm{C}_a–\mathrm{C}_c \) bond (see Scheme 1B). Rotation around this bond is supposed to be rather fixed by the geminal-diaryl effect.\(^ {39a} \) Again, the available conformational information has been limited to crystal structure analyses\(^ {39a} \) and to theoretical calculations.\(^ {39b,41,43-45} \) However, because of the lack of experimental data in solution, partially conflicting results have been put forward, in particular whether the sc-exo\(^ {39b,45} \) or the sc-endo\(^ {41,43,44} \) conformation of diarylprolinol ether enamines constitutes the better structural basis for intermediate and transition state calculations. This also holds true for (diaryl)prolinol-derived enamines, for which two opposite modes of stereoselection have been claimed: steric shielding of one face of the enamine by the aryl rings\(^ {39a} \) on the one hand and direction of the electrophile to this face of the enamine via an H-bond\(^ {55,37} \) on the other hand. Knowledge of the rotation around the \( \mathrm{C}_a–\mathrm{C}_c \) bond should also help to shed some light on this issue.

**Determination of conformational preferences by NOESY spectra.** There are three different staggered conformations for the exocyclic \( \mathrm{C}_a–\mathrm{C}_c \) bond (Fig. 3A), termed sc-endo, sc-exo and ap. In general, the stereoelectronic preference of 1,2-electron-negatively disubstituted ethane moieties, such as N–C–C–O, to adopt a synclinal conformation (commonly referred to as the gauche effect)\(^ {68,69} \) is expected to favor the sc-endo and sc-exo conformations over the ap conformation. To determine which of these conformations is really preferentially populated by prolinol (ether) enamines in solution, enamines 1a–7b were investigated in different solvents by means of NMR spectroscopy. The sc-endo, sc-exo and ap conformations can, in principle, be distinguished by their associated NOE intensity patterns obtained from the \( ^{1} \mathrm{H},^{1} \mathrm{H} \)-NOESY spectra, in particular, as gauche-oriented vicinal substituents should give rise to larger NOEs than ap-oriented vicinal substituents. Thereby, the investigation of the NOEs of the OH/OR-substituent protons proved to be valuable to determine the preferred conformation at the \( \mathrm{C}_a–\mathrm{C}_c \) bond. Fig. 3B shows example sections from the \( ^{1} \mathrm{H},^{1} \mathrm{H} \)-NOESY spectra of 3b (left) and 5b (right) in DMSO-\( \mathrm{d}_6 \) at 300 K.

The spectral sections of 3b reveal significantly stronger NOEs from \( \mathrm{OH} \) to \( \mathrm{H}\beta_2 \) and \( \mathrm{H}_2 \gamma \) than to \( \mathrm{H}_z \) and a stronger NOE of \( \mathrm{H}_2 \gamma \) to \( \mathrm{OH} \) than to the aromatic protons of the phenyl rings (Fig. 3b, left). This NOE pattern is best explained by an sc-endo conformation of the \( \mathrm{C}_a–\mathrm{C}_c \) bond in the case of 3b. In contrast, for 5b, the protons of OMe show much stronger NOEs to \( \mathrm{H}_1 \) and \( \mathrm{H}_z \) than to \( \mathrm{H}\beta_2 \) or \( \mathrm{H}_2 \gamma \) and, vice versa, a stronger NOE from \( \mathrm{H}_2 \gamma \) to the aromatic protons than to the protons of OMe was observed (Fig. 3B, right). These findings for 5b are indicative of an sc-exo conformation around the exocyclic \( \mathrm{C}_a–\mathrm{C}_c \) bond. In line with the gauche effect, the preferential adoption of the ap conformation, however, can be ruled out on the basis of these NOE intensity patterns in both cases.

**Conformational screening approach.** Since the conformation of the exocyclic \( \mathrm{C}_a–\mathrm{C}_c \) bond is of high importance for the understanding of the stereocontrol exerted by diphenylprolinol (ether) organocatalysts, we intended to develop a facile and rapid way to screen enamines for the \( \mathrm{C}_a–\mathrm{C}_c \) conformation without the need to record and analyze NOESY spectra. In this context, we could observe that the two different preferred conformations of the \( \mathrm{C}_a–\mathrm{C}_c \) bond in 3b and 5b are also reflected in a very characteristic way by the \( ^{1} \mathrm{H} \) chemical shifts. For the sc-endo conformation of 3b, a significant upfield-shift of \( \mathrm{H}_1 \), relative to 1b as a ring current-free reference compound, was found (\( \delta = 5.37 \) ppm, \( \Delta \delta = 0.81 \) ppm), whereas in the case of the sc-exo conformation of 5b the protons on the “upper” face of the pyrrolidine ring \( \mathrm{H}_2 \gamma \) and \( \mathrm{H}\beta_2 \) are remarkably shielded (\( \delta = 0.01 \) and 2.37 ppm, \( \Delta \delta = 1.75 \) and 0.61 ppm, respectively). These characteristic and highly remarkable chemical shift differences of 3b and 5b compared to the corresponding values of 1b (see Fig. 4A for a visualization and the \( ^{1} \mathrm{H} \) NMR assignments) suggests that the upfield shifts are caused by ring current effects. The observation of such shifted CH protons in the presence of aromatic rings is well-known in terms of the ASIS (aromatic solvent-induced shift)\(^ {59} \) and is rationalized by the Bovey model,\(^ {71} \) which predicts the deshielding of protons outside the ring current, but shielding of those within it. Upfield-shifted proton resonances in the presence of aromatic moieties can therefore be interpreted as an indication of CH/\( \pi \) interactions.\(^ {55} \) This interpretation is in very good agreement with the s-trans enamine arrangement and the preference of the pyrrolidine down conformation discussed above, as shown by the structure models for 3b and 5b (Fig. 4B). These geometric models (reined with molecular mechanics, MMFF force field) are based on the down conformation of the pyrrolidine ring, the s-trans arrangement of the enamine moiety and the sc-endo or sc-exo conformation around the \( \mathrm{C}_a–\mathrm{C}_c \) bond, respectively. They reveal

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that the \textit{sc-endo} conformation in \textit{3b} may be stabilized by an OH···N hydrogen bond and may also be effortlessly accompanied by a H1–Ph interaction. In contrast, for the \textit{sc-exo} conformation of \textit{5b}, an interaction between H\textsubscript{72} (also H\textsubscript{52}) and Ph is achieved straightforwardly; all of these CH··π interactions correspond well with the observation of the selectively upfield-shifted proton resonances. It is also important to note that in the \textit{sc-exo} conformation, the steric shielding of the “upper” face of the enamine is effectuated by both the aromatic ring (in particular its \textit{meta}-substituent) and the O-protecting group.\textsuperscript{39} The associated steric conflicts should, to a certain degree, destabilize the enamine and, in fact, this is in striking agreement with our observation on decreasing prolinol ether enamine amounts with increasing sizes of the aryl \textit{meta}-substituent and the O-protecting group.\textsuperscript{46} Hence, our NMR spectroscopic findings concerning the various conformational aspects of diarylprolinol (ether) enamines show excellent consistency and indicate the conformations of Fig. 4B as the preferred ones for \textit{3b} and \textit{5b} in DMSO-\textit{d6}.

In contrast to all of the enamines studied, neither the conformational fixation of the pyrrolidine ring (see above) nor the upfield-shifts of individual protons are observed for the free catalysts \textit{2}–\textit{7} (see Schemes S3 and S4 in the Supplementary Information\textsuperscript{†}). One may thus assume that the predictive value of conformational studies on prolinol (ether) organocatalysts for the conformations of their enamine intermediates is rather limited. Instead, our investigations stress the importance of performing conformational studies on the actual organocatalytic intermediates themselves as reliable starting points for theoretical calculations of the reaction pathways and transition state conformations (see discussion below). In addition, the simultaneous appearance of the conformational preferences of the pyrrolidine ring and around the C\textsubscript{x}–C\textsubscript{e} bond in prolinol (ether) enamine intermediates strongly suggest stabilizing interactions between the pyrrolidine ring and the methanol ether substituents (in agreement with the interactions discussed above and shown in Fig. 4).

On the basis of their excellent correspondence with the \textit{sc-endo} or \textit{sc-exo} conformation around the exocyclic C\textsubscript{x}–C\textsubscript{e} bond, the upfield-shifts of protons H1 or H\textsubscript{72} and H\textsubscript{52}, respectively, in the enamine intermediates can be used as a facile method to rapidly screen diarylprolinol-derived enamines for the orientation of the bulky diarylmethanol substituent. As the case of the \textit{ap} conformation can be ruled out as the major conformation, as revealed for all of the enamines studied (see below), the chemical shifts for H1 of 5.20–5.42 ppm are indicative of the \textit{sc-endo} conformation, while H\textsubscript{72} and H\textsubscript{52} resonances in the ranges 0.00–0.35 ppm and 2.20–2.40 ppm, respectively, evidence the \textit{sc-exo} conformation.

**Generality of the conformational preferences.** The most striking aspect of the comparison of \textit{3b} and \textit{5b} is the conformational switch from \textit{sc-endo} (\textit{3b}) to \textit{sc-exo} (\textit{5b}) upon protection of the OH functionality of \textit{3b}. We therefore investigated the generality of this conformational change as a first application and test of our screening method for the conformation around the C\textsubscript{x}–C\textsubscript{e} bond. For that purpose, enamines \textit{1a}–\textit{7b}, derived from different aldehydes and different catalysts, were studied in DMSO-\textit{d6} by NMR spectroscopy. Subsequently, enamines \textit{5b} and \textit{7b} were investigated in other solvents too. The 1D 1\textsuperscript{H} screening results were verified by NOESY analyses wherever possible (Tables 2 and 3).

We first examined the potential influences of the catalyst structure and the aldehyde alkyl chain on the C\textsubscript{x}–C\textsubscript{e} conformation (Table 2). By comparison to the ring current-free enamines \textit{1a} and \textit{1b}, upfield shifts of the H1-resonance in all of the \textit{O}-unprotected enamines \textit{2a}–\textit{4b} become evident, as well as upfield shifts of the H\textsubscript{72}/H\textsubscript{52}-resonances of all of the \textit{O}-protected enamines \textit{5a}–\textit{7b} (entries in Table 2 highlighted in grey). As verified in most cases by NOESY analyses, these shifts

![Fig. 4](image-url)
are indicative of the sc-endo conformation for all of the diarylprolinol enamines (2a–4b) and of the sc-exo conformation for all of the diarylprolinol ether enamines (5a–7b).

In addition, the possible solvent effects on the preferred population of these conformations were investigated (Table 3). As the detection of prolinol enamines was only successful in DMSO-d$_6$, these solvent studies were performed for only the diarylprolinol ether enamines (5a–7b).

The characteristic upfield-shifts of H$_2$/H$_3$ were found in all of the solvents applied, ranging from polar aprotic (DMSO-d$_6$, MeCN-d$_3$) over polar protic (MeOH-d$_4$) to nonpolar (CDCl$_3$) and aromatic solvents (PhMe-d$_8$). This indicates that solvent properties do not affect the conformational preferences around the C$_{z}$–C$_{c}$ bond of diarylprolinol ether enamines.

Altogether, our straightforward $^1$H NMR screening method, backed by NOESY analyses, shows that the protection of the hydroxyl group is the decisive factor for the conformational switch observed from diarylprolinol enamines (sc-endo) to diarylprolinol ether enamines (sc-exo). In contrast, neither the nature of the protecting group (Me or TMS, cf. 5a,b with 6a,b), nor the nature of the aromatic rings (Ph or Ar, cf. 3a,b with 2a,b and 4a,b or cf. 6a,b and 7a,b), nor the size of the aldehyde alkyl chain (Pr or Me, cf. 2a–7a with 2b–7b) seem to be of greater conformational importance. Moreover, the sc-exo conformation is preferred by diarylprolinol ethers independent of the solvent used. Thus, from a conformational point of view, the etherification of the hydroxyl group of prolinols does not only have a significant impact on the stability of the corresponding enamines, but also on the orientation of the bulky pyrrolidine $\alpha$-substituent.

### Discussion of the conformational preferences

Our NMR observation of the sc-exo conformation for diarylprolinol ether enamines in solution is not only in agreement with the available enamine crystal structure, but also enables the interpretation of previous reported NMR data on comparable enamine species. Following our $^1$H chemical shift screening criterion for C$_{z}$–C$_{c}$ conformation of diarylprolinol ether enamines. They clearly evidence the sc-exo conformation of s-trans diarylprolinol ether enamines in solution and thus, in agreement with a comparative theoretical study from Seebach’s group, back the sc-exo conformation and reject the sc-endo conformation as the proper basis for enamine intermediate calculations.

Beyond the determination of intermediate conformations, we believe our study is also relevant to the calculation and investigation of organocatalytic reaction pathways. In addition, our study allows the identification of theoretical studies that are in agreement with the structural properties, being valid in solution.

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**Table 2** Characteristic $^1$H chemical shifts of enamines 1a–7b in DMSO and correlations to the conformation around the exocyclic C$_{z}$–C$_{c}$ bond.

<table>
<thead>
<tr>
<th>Enamine</th>
<th>H1</th>
<th>H2</th>
<th>H3</th>
<th>NOESY-based conformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>6.17</td>
<td>1.75–1.45$^a$</td>
<td>2.97</td>
<td>n. ass.$^b$</td>
</tr>
<tr>
<td>1b</td>
<td>6.18</td>
<td>1.76</td>
<td>2.98</td>
<td>n. ass.$^b$</td>
</tr>
<tr>
<td>2a</td>
<td>5.27</td>
<td>1.80–1.35$^a$</td>
<td>3.07</td>
<td>n. det.</td>
</tr>
<tr>
<td>2b</td>
<td>5.42</td>
<td>1.65–1.35$^a$</td>
<td>3.04</td>
<td>n. det.</td>
</tr>
<tr>
<td>3a</td>
<td>5.26</td>
<td>1.55</td>
<td>3.06</td>
<td>sc-exo</td>
</tr>
<tr>
<td>3b</td>
<td>5.37</td>
<td>1.50</td>
<td>3.02</td>
<td>sc-exo</td>
</tr>
<tr>
<td>4a</td>
<td>5.20</td>
<td>1.65–1.35$^a$</td>
<td>3.11</td>
<td>n. det.</td>
</tr>
<tr>
<td>4b</td>
<td>5.37</td>
<td>1.65–1.35$^a$</td>
<td>3.09</td>
<td>n. det.</td>
</tr>
<tr>
<td>5a</td>
<td>5.94</td>
<td>0.01</td>
<td>2.37</td>
<td>sc-exo</td>
</tr>
<tr>
<td>5b</td>
<td>6.06</td>
<td>0.01</td>
<td>2.37</td>
<td>sc-exo</td>
</tr>
<tr>
<td>6a</td>
<td>6.19</td>
<td>0.34</td>
<td>2.33</td>
<td>sc-exo</td>
</tr>
<tr>
<td>6b</td>
<td>6.29</td>
<td>0.25</td>
<td>2.34</td>
<td>sc-exo</td>
</tr>
<tr>
<td>7a</td>
<td>6.05</td>
<td>0.30</td>
<td>2.23</td>
<td>n. det.</td>
</tr>
<tr>
<td>7b</td>
<td>6.22</td>
<td>0.25</td>
<td>2.27</td>
<td>sc-exo</td>
</tr>
</tbody>
</table>

$^a$ Only the chemical shift ranges can be given because of severe resonance overlap. $^b$ Spectral overlap prevented the determination of the conformation. $^c$ n. ass. = not assignable; n. det. = not determined.

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**Table 3** Characteristic $^1$H chemical shifts of enamines 5b and 7b in different solvents and their correlations to the conformation around the exocyclic C$_{z}$–C$_{c}$ bond.

<table>
<thead>
<tr>
<th>Enamine</th>
<th>Solvent</th>
<th>H1</th>
<th>H2</th>
<th>H3</th>
<th>NOESY-based conformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>5b</td>
<td>DMSO-d$_6$</td>
<td>6.06</td>
<td>0.01</td>
<td>2.37</td>
<td>sc-exo</td>
</tr>
<tr>
<td></td>
<td>MeCN-d$_3$</td>
<td>6.14</td>
<td>0.08</td>
<td>2.43</td>
<td>n. det.</td>
</tr>
<tr>
<td></td>
<td>MeOH-d$_4$</td>
<td>6.10</td>
<td>0.14</td>
<td>2.44</td>
<td>n. det.</td>
</tr>
<tr>
<td></td>
<td>CDCl$_3$</td>
<td>6.11</td>
<td>0.10</td>
<td>2.48</td>
<td>sc-exo</td>
</tr>
<tr>
<td></td>
<td>PhMe-d$_8$</td>
<td>6.31</td>
<td>0.22</td>
<td>2.53</td>
<td>n. det.</td>
</tr>
<tr>
<td>7b</td>
<td>DMSO-d$_6$</td>
<td>6.22</td>
<td>0.25</td>
<td>2.27</td>
<td>sc-exo</td>
</tr>
<tr>
<td></td>
<td>PhMe-d$_8$</td>
<td>6.12</td>
<td>0.09</td>
<td>2.26</td>
<td>n. det.</td>
</tr>
</tbody>
</table>

$^a$ n. det. = not determined.
For instance, a recent DFT calculation on the transition state for the asymmetric Michael addition of 5b to methyl vinyl ketone features all of the conformational properties of the enamine intermediate that we determined experimentally; the E-configuration of the enamine double-bond, the s-trans arrangement of the enamine, the down conformation of the pyrrolidine ring and the sc-exo conformation of the ω-substituent around the Cα–Cβ bond. Accordingly, the electrophilic attack of vinyl methyl ketone to the enamine occurs from the convex half-space opposite the “obese” diphenylmethoxymethyl substituent of 5b. As previously pointed out, in the sc-exo conformation of diarylprolinol ether enamine intermediates, the steric shielding of one face of the enamine is secured by both the meta-substituents of the aryl groups and the O-protecting group. Thus, increasing stereoselectivities in asymmetric reactions should be obtained by enlarging either the aryl meta-substituent or the O-protecting group of the organocatalyst. Indeed, this effect has been regularly reported for increasing sizes of the aryl meta-substituent and the O-protecting group. In addition, our finding of a stable sc-exo Cα–Cβ conformation predicts that the enlargement of only one of the two phenyl rings should be sufficient to increase the shielding of one face of the enamine and hence to increase the stereoselectivity. In fact, such an effect has been recently observed. All this data suggests that the sc-exo 48 conformation and not the sc-endo 44–45 conformation is also predominant in transition states involving diarylprolinol ether enamines, which may be confirmed by further theoretical calculations based on this experimental study.

Our first experimental data on prolinol enamine intermediate conformations might be a useful guide for further theoretical investigations on the origin of stereocntrol by diarylprolinol enamines, despite their rather limited applicability. Still, it is interesting to note that for prolinol enamines two different modes of stereocntrol in the bond-forming transition state have been postulated. On the one hand, steric shielding of the “upper” enamine face by the bulky substituent has been proposed and, on the other hand, a directing function of the hydroxyl group via H-bonding interactions to the electrophile on this “upper” face has been claimed. Interestingly, the sc-endo conformation around the Cα–Cβ bond of diarylprolinol enamines that we observed in this study allows for both a H-bond from the hydroxyl group to an incoming electrophile and steric shielding by one of the aryl rings. Thus, both interactions may indeed contribute as stereodirecting factors. Nevertheless, since the change of the sc-endo conformation in diarylprolinol enamines to sc-exo in diarylprolinol ether enamines is apparently triggered by the protection of the OH-functionality, a special role in the stabilization of the sc-endo conformation can be attributed to the OH group. This is in agreement with a previous study that shows that prolinol enamines may develop an N···HO hydrogen bond only in the sc-endo conformation (note: N is to be taken as a representative of the enamine π system as a hydrogen bond acceptor). In the case of our simple structure model of Fig. 4B (d(N···H) = 2.1 Å, d(N···O) = 2.7 Å, <(N···H–O) = 122°), this hydrogen bond in 3b is to be classified as weak to moderate, but it might be sufficient to cause the preference of the sc-endo conformation. In solvents with lower H-bond acceptor abilities than DMSO, the favourable energetic contribution of this H-bond should be even more pronounced.

Moreover, the upfield-shift of the H1 resonance (see above) indicates an additional CH/π contribution between H1 and one of the phenyl rings that also stabilizes the sc-endo conformation of diarylprolinol derivatives (Fig. 4B, top). For the further rationalization of the sc-endo conformation, the stronger steric repulsion between the pyrrolidine hydrogens and the aryl rings compared to the OH-group has been claimed previously. This would imply that the sc-exo conformation in diarylprolinol ether enamines should be switchable to sc-endo either by reducing the size of the O-protecting group (Me instead of TMS) or by increasing the size of the aromatic rings (Ar instead of Ph); yet, in none of these cases did we observe a change of the preferred sc-exo conformation towards sc-endo. This makes us believe that steric clashes are of minor importance for the issue of conformational preferences around the Cα–Cβ bond. Thus, it is highly likely that the weak conformation-stabilizing intramolecular interactions account for the observed preferences of the sc-endo and the sc-exo conformations of diarylprolinol (ether) enamines. For diarylprolinol enamines, we found evidence for a N···HO hydrogen bond and one CH/π interaction and in diarylprolinol ether enamines strong experimental evidence for two CH/π interactions is provided. Thus, for the first time, CH/π interactions are suggested as a conformation-determining factor for enamine intermediates in organocatalysis. It is notable that upfield-shifted pyrrolidine protons have also been reported for diarylprolinol ether iminium salts, which, in combination with the crystallographic data, may be interpreted in terms of similar CH/π interactions being operative and structure-determining in iminium ions too.

**Graphical summary of the conformational preferences and NMR screening methods**

The crucial conformational aspects of diarylprolinol (ether) enamines (orientation of the ene moiety, pyrrolidine puckering and rotation of the bulky diarylmethanethiol substituent) can be straightforwardly screened for by means of NMR spectroscopy.

![](https://example.com/graph.png)

**Fig. 5** A graphical summary of the conformational preferences and NMR screening methods for prolinol (ether) enamines.
For the sake of clarity, the results and approaches outlined above are summarized graphically in Fig. 5.

Conclusions
In summary, we present the first detailed conformational investigations on enamines derived from prolinol and prolinol ether-type organocatalysts, with two different aldehydes in various solvents, by means of NMR spectroscopy. Concerning the exocyclic N–C bond, we report the first NOESY-based experimental proof that a prolinol-derived enamine partially exists in the s-cis conformation in solution. For diarylprolinol ether enamines in contrast, only the s-trans conformation is observed in solution most probably owing to the bulkiness of the pyrrolidine a-substituent. In addition, for all of the enamines studied, enamine formation is associated with a strong preference for the down conformation of the pyrrolidine ring. For the rotation around the exocyclic Cα–Cε bond, diarylprolinol enamines are found by NOESY analyses to be present in the sc-endo conformation, while the diarylprolinol ether enamines adopt the sc-exo conformation. Strong experimental evidence is provided that the sc-exo conformation in diarylprolinol ether enamines is stabilized by CHπ interactions between the aliphatic hydrogen atoms of the pyrrolidine ring in the down conformation and an aromatic π system of the bulky pyrrolidine a-substituent. In addition, a rapid conformational screening method, based on H chemical shifts, was developed and applied to show the generality of these conformational preferences for various catalysts, aldehydes and solvents.

The broad experimental basis provided in this study and our observation of the exquisite conformational preferences of enamine intermediates in solution experimentally clarify the hitherto contradictory postulations and unsolved issues of s-cis/s-trans and sc-endo/sc-exo enamine conformations. Thus, the presented conformational features help to explain the experimental performances of various catalysts, promote the rationalization of the stereochemical outcome and facilitate further catalyst optimization.

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Notes and references
3 Special Issue on Organocatalysis, Chem. Rev., 2007, 107, 12.