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EDGE ARTICLE

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 stereocontrol 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 acids[12,13] 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 amines[15–17] through enamine,[18,19] iminium,[20,21] or SOMO[22–24] activation has emerged as one of the most successful and widely applicable principles. In particular, proline[25–27] and Jørgensen–Hayashi-type prolinol ethers[28–33] have been proven to give remarkable performances in asymmetric iminium and enamine organocatalysis. Also, prolinol organocatalysts[34] have found a use based on enamine intermediates,[35–38] 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 isolated and characterized,[39,40] while only one dienamine intermediate[41] and one product enamine[42] have been observed *in situ*. Therefore, the conformations of such enamine intermediates in solution are largely unknown and conformational information

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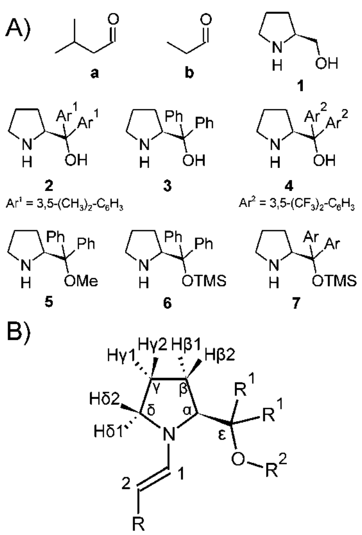
has, so far, been limited to theoretical calculations[39b,41,43–45] and crystal structure analyses[39]. However, these approaches may be affected by vacuum calculation artifacts or crystal packing effects. Accordingly, conflicting results concerning the conformational preferences of both the exocyclic N–C bond[39,41,43–46] and the exocyclic C–C bond[39b,41,43–45] 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[47] and prolinols[46] and by various aldehyde-derived prolinol ether enamines.[46] 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. ^{1}H,^{1}H-NOESY spectra reveal the preference of the enamine s-*trans* arrangement due to the steric influence of the pyrrolidine α-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" α-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 ^{1}H 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.



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

Results and discussion

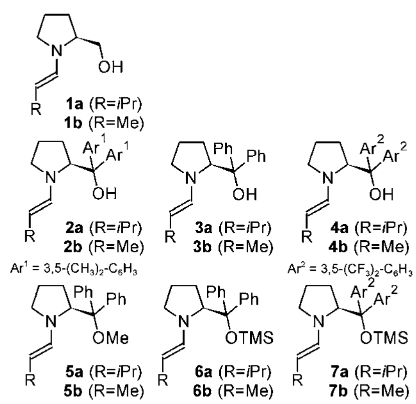
Model enamines

On the basis of our recent studies on proline enamines[47] and on the formation and stability of prolinol (ether) enamines[46] in solution, various typical secondary amine organocatalysts (Scheme 1: **1–7**)[28–30] 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**)[47] 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.[46] 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.[46] (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,[46] 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[39b,41,43–45] and crystal structure analyses,[39] and in agreement with previous experimental results, it is generally assumed that the methanol(ether)-substituent of the



Scheme 2 The investigated *E*-enamines derived from aldehydes **a** and **b** and catalysts **1–7**, displayed in the favorable s-*trans* conformation.

pyrrolidine 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.[39b] 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 ^{1}H,^{1}H-NOESY spectra. Addressing the conformational preferences of the pyrrolidine ring and of the exocyclic N–C1 and Cα–Cε 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**.[39b] 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).[39b] The guarantee of this basic conformational feature of the enamine key intermediate by the bulky α-substituent 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.[46] The predominance of the s-*trans* conformation in the case of proline enamines has been proposed from calculations[48] and has been experimentally proven by our NMR studies in solution;[47] in addition, exclusively s-*trans* proline enamines have been detected in crystal structures.[49] Likewise for prolinol ether enamines, the s-*trans* conformation has been observed in crystal structures[39] and its energetic preference has been thoroughly calculated.[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.[44]

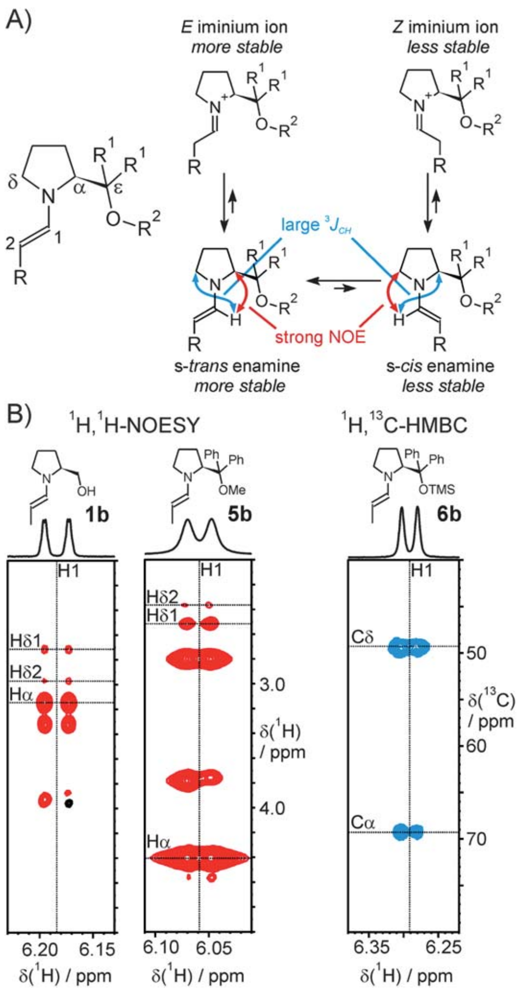
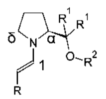


Fig. 1 A) Left: atom nomenclature; right: the equilibrium between the enamine conformations, their relation to iminium ions and the distinctive NOEs and $^3J_{CH}$; B) Sections of the ^{1}H,^{1}H-NOESY spectra of **1b** (left) and **5b** (middle) and of a ^{1}H,^{13}C-HMBC spectrum of **6b** (right) in DMSO-d_6 at 300 K.

To experimentally clarify this issue in solution, we analyzed the ^{1}H,^{1}H-NOESY spectra of enamines **1b–7b** (example sections are shown in Fig. 1B). The relative intensities of the NOEs between H1 and the protons Hα 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 Hα is expected, while a stronger NOE between H1 and Hδ1,2 would be indicative of a predominant population of the s-*cis* conformation. The ^{1}H,^{13}C-HMBC cross-peak intensities between H1 and Cα or Cδ can be used as an additional criterion, since $^3J_{CH}$ couplings are known to be larger in an antiperiplanar than in a synperiplanar arrangement.[50] 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 Hα 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 pyrrolidines and different aldehydes in both polar and non-polar solutions. This finding was confirmed by the ^{1}H,^{13}C-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 $^3J_{HC}$ 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 Hα was compared to the sum of the cross-peak volumes between H1 and Hδ1,2. The larger the ratio NOE(H1–Hα):NOEs(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–Hα):NOEs(H1–Hδ1,2) for a pure s-*trans* enamine was

Table 1 Experimental NOESY cross-peak volumes for the various enamines[a] and theoretical values based on the calculated[44,45] s-*trans* enamine structures



	Normalized NOESY cross-peak volumes				
	Experimental values			Theoretical values (s-*trans* enamines)	
NOE pair	**1b**	**5b**, **6b**, **7b**	**5a**, **6a**	**6b**[45]	**7b**[44]
	R^1 = H R^2 = H R = Me	R^1 = Ar R^2 = Me/TMS R = Me	R^1 = Ph R^2 = Me/TMS R = *i*Pr	R^1 = Ph R^2 = TMS R = Me	R^1 = Ar^2 R^2 = TMS R = Me
H1-Hα	≤79[b]	91–94	90–91	88	92
H1–Hδ1 + H1–Hδ2	≥21[b]	6–9	9–10	12	8

[a] 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.[44,45] 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.[46] 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(H1–Hα):NOEs(H1–Hδ1,2), 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.[46]

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.[51] This previous lack of interest is striking in view of the fact that the pyrrolidine ring is known to be an important structure,[27,52–54] 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".[39] 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[55–57] with the phenyl rings in diarylprolinol (ether) enamines; these weak interactions have been proven to have important implications not only in biochemistry,[58,59] but also in molecular recognition and organic chemistry.[60–63] Secondly, in general, different pyrrolidine ring conformations may well be associated with different reactivities[64] and the catalytic performances of the respective compounds.[65] In particular, in diarylprolinol ether enamines the pyrrolidine *up* conformation, in combination with the known slight pyramidality of the enamine nitrogen atom,[39–41,43–45,51] 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, in 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.

As a basis for studying the pyrrolidine conformation in prolinol (ether) enamines, the previous extensive investigations on proline side-chain conformations could be used. For proline residues in peptides and proteins, it has been established that two distinct pyrrolidine envelope conformations are preferentially adopted, commonly designated as "*up*" and "*down*" (Fig. 2A). This simple two-state model for the pyrrolidine ring in proline should be readily transferable to prolinol (ether) enamines, since approximate planarity may be assumed for both the amide group

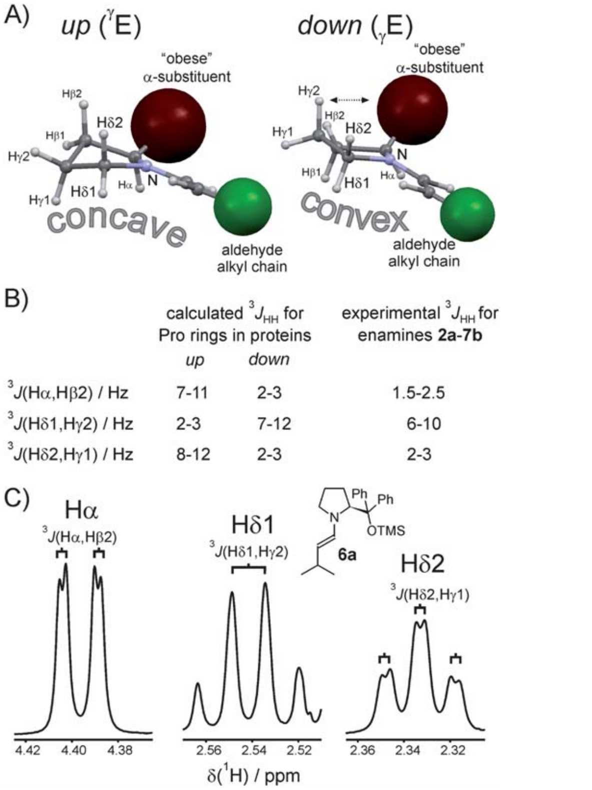


Fig. 2 A) The two low-energy pyrrolidine conformations "*up*" and "*down*". B) Distinguishing the calculated $^3J_{HH}$ coupling constants for the *up* and *down* conformations of proline residues in proteins[66] and the experimental range for the enamines investigated in this study. C) Sections of the 1D ^{1}H NMR spectrum of **6a** in DMSO-d_6 at 300 K showing the typical multiplet patterns for Hα, Hδ1 and Hδ2 observed in diarylprolinol (ether) enamines.

in peptides and the enamine moiety in organocatalytically active intermediates (on the basis of prolinol ether enamine crystal structures[39] and DFT calculations[39b,41,43–45]). 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 ^3J(Hα,Hβ1/2), potentially caused by the different Cε-substituents, is observed for the free catalysts proline and **2–7** (see Schemes S3 and S4 in the supplementary information†). The two different pyrrolidine conformations *up*/*down* can be distinguished by NMR *via* their characteristic $^3J_{HH}$,[66] which are easily extracted from well-resolved ^{1}H resonance multiplet patterns. Accordingly, small ^3J(Hα,Hβ2) and ^3J(Hδ2,Hγ1) indicate the population of the *down* conformation, while small ^3J(Hδ1,Hγ2) are indicative of the *up* conformation. The two conformations *up*/*down* and the associated theoretical and experimentally observed $^3J_{HH}$ 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 ^3J(Hα,Hβ2) and ^3J(Hδ2,Hγ1), (not only in DMSO-d_6, but also in MeCN-d_3, $CDCl_3$ and PhMe-d_8, see Scheme S1 in the supplementary information†). In contrast, values in the range 6–10 Hz were detected for ^3J(Hδ1,Hγ2), which leads to the characteristic multiplet patterns depicted in Fig. 2C for the example of **6a**. (Unfortunately, coupling constants could not be extracted for **1a** and **1b** due to spectral overlap and higher order NMR signals.) The experimental values for ^3J(Hα,Hβ2) and ^3J(Hδ2,Hγ1) equal those expected for the pure *down* conformation.[66] This indicates the *down* conformation for the pyrrolidine ring in diarylprolinol (ether) enamines in solvents ranging from DMSO over MeCN to $CHCl_3$ and PhMe. In addition, the small ^3J(Hα,Hβ2) and ^3J(Hδ2,Hγ1) show that conformations with large coupling constants, *e.g. up*, do not substantially contribute to the conformational ensemble, which can be taken as an indication of a rather stable structure.[67] Interestingly, for the aldol transition states of the proline-derived catalysts, the theoretical calculations suggested that the *down* conformation is significantly preferred only for β-substituted pyrrolidine rings.[51] However, our experimental study reveals a high preference for the *down* conformation, even in the absence of β-substituents. In contrast, in free catalysts **2–7**, both ^3J(Hα,Hβ1/2) are larger than 7 Hz, which indicates a dynamic equilibrium of the *up* and *down* conformations (see Schemes S3 and S4† and the exemplary Hα multiplets in Fig. 3C of our previous report.[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 α-substituent, imposes conformational constraints on the pyrrolidine ring to such a degree that one pyrrolidine conformation (*down*) is exclusively observed. As a first assumption, this may be rationalized by the

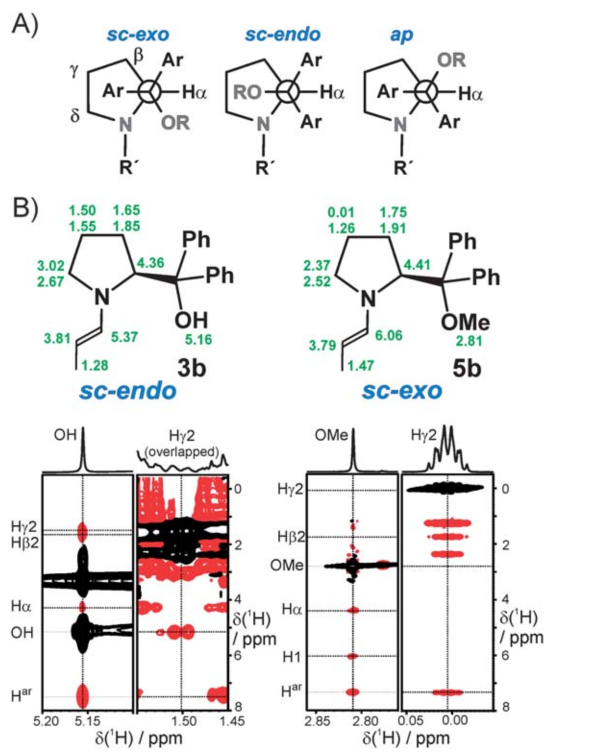


Fig. 3 A) Staggered conformations of diarylprolinol (ether) enamines. B) ^{1}H NMR assignments of **3b** (left) and **5b** (right) (note: the chemical shifts of Hβ1, Hγ1 and Hδ1 are listed below those of Hβ2, Hγ2 and Hδ2) and sections of their ^{1}H,^{1}H-NOESY spectra (bottom) in DMSO-d_6 at 300 K (intensities of the sections are scaled individually for optimum clarity).

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" α-substituent and the vicinal β, as well as the δ 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[39] 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.[51] In addition, it is only the *down* conformation that creates sufficient spatial proximity between the methanol ether substituents and the Hγ2 of the pyrrolidine ring (Fig. 2A) to potentially allow for stabilizing CH/π 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 Cα–Cε bond: *sc-exo*, *sc-endo* and *ap*

The effective shielding of one face of the enamine π 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**.[39b] 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 Cα–Cε 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[36] on the one hand and direction of the electrophile to this face of the enamine *via* an H-bond[35,37] on the other hand. Knowledge of the rotation around the Cα–Cε 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 Cα–Cε bond (Fig. 3A), termed *sc-endo*, *sc-exo* and *ap*. In general, the stereoelectronic preference of 1,2 electronegatively 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}H,^{1}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 Cα–Cε bond. Fig. 3B shows example sections from the ^{1}H,^{1}H-NOESY spectra of **3b** (left) and **5b** (right) in DMSO-d_6 at 300 K.

The spectral sections of **3b** reveal significantly stronger NOEs from OH to Hβ2 and Hγ2 than to Hα and a stronger NOE of Hγ2 to 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 Cα–Cε bond in the case of **3b**. In contrast, for **5b**, the protons of OMe show much stronger NOEs to H1 and Hα than to Hβ2 or Hγ2 and, *vice versa*, a stronger NOE from Hγ2 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 Cα–Cε 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 Cα–Cε 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 Cα–Cε conformation without the need to record and analyze NOESY spectra. In this context, we could observe that the two different preferred conformations of the Cα–Cε bond in **3b** and **5b** are also reflected in a very characteristic way by the ^{1}H chemical shifts. For the *sc-endo* conformation of **3b**, a significant upfield-shift of H1, 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 Hγ2 and Hδ2 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}H NMR assignments) suggests that the upfield shifts are caused by ring current effects. The observation of such shielded CH protons in the presence of aromatic rings is well-known in terms of the ASIS (aromatic solvent-induced shift)[70] 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/π 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 (refined 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 Cα–Cε bond, respectively. They reveal

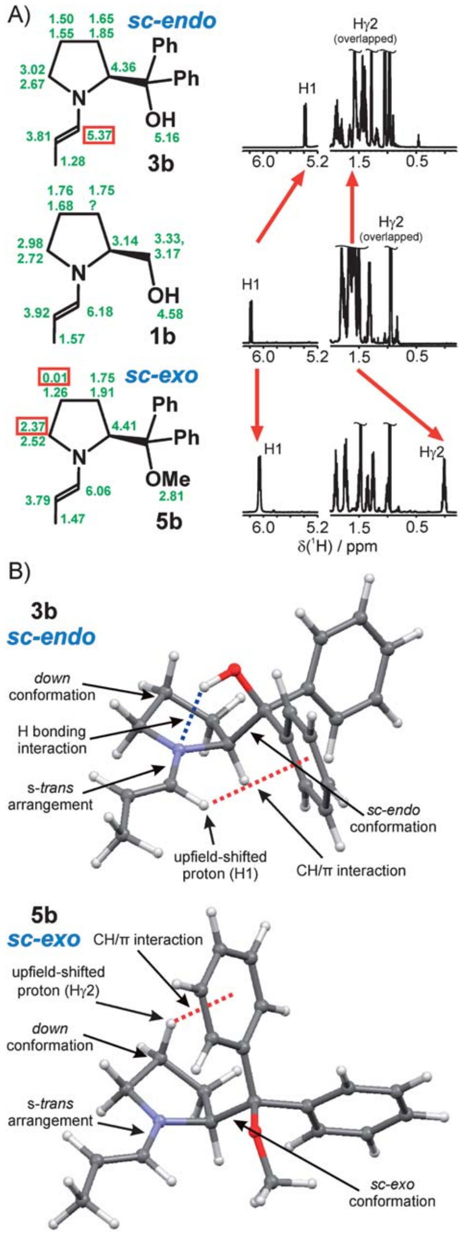


Fig. 4 A) ^{1}H chemical shifts of **3b**, **1b**, and **5b** in DMSO-d_6 with upfield-shifted resonances highlighted in red (left) and sections of the corresponding ^{1}H NMR spectra (right). (Hβ1, Hγ1 and Hδ1 are listed below Hβ2, Hγ2 and Hδ2. For **1b**, the Cα–Cε conformation is not accessible because of signal overlap.) B) MMFF-refined structure models of **3b** and **5b** based on the NMR-derived conformational features.

that the *sc-endo* conformation in **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 *sc-exo* conformation of **5b**, an interaction between Hγ2 (also Hδ2) 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 *sc-exo* conformation, the steric shielding of the "upper" face of the enamine is effectuated by both the aromatic ring (in particular its *meta*-substituent) and the *O*-protecting group.[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 *meta*-substituent and the *O*-protecting group.[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 **3b** and **5b** in DMSO-d_6.

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 **2–7** (see Schemes S3 and S4 in the Supplementary Information†). 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 Cα–Cε 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 *sc-endo* or *sc-exo* conformation around the exocyclic Cα–Cε bond, the upfield-shifts of protons H1 or Hγ2 and Hδ2, 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 *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 *sc-endo* conformation, while Hγ2 and Hδ2 resonances in the ranges 0.00–0.35 ppm and 2.20–2.40 ppm, respectively, evidence the *sc-exo* conformation.

Generality of the conformational preferences. The most striking aspect of the comparison of **3b** and **5b** is the conformational switch from *sc-endo* (**3b**) to *sc-exo* (**5b**) upon protection of the OH functionality of **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 Cα–Cε bond. For that purpose, enamines **1a–7b**, derived from different aldehydes and different catalysts, were studied in DMSO-d_6 by NMR spectroscopy. Subsequently, enamines **5b** and **7b** were investigated in other solvents too. The 1D ^{1}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 Cα–Cε conformation (Table 2). By comparison to the ring current-free enamines **1a** and **1b**, upfield shifts of the H1-resonance in all of the *O*-unprotected enamines **2a–4b** become evident, as well as upfield shifts of the Hγ2/Hδ2-resonances of all of the *O*-protected enamines **5a–7b** (entries in Table 2 highlighted in grey). As verified in most cases by NOESY analyses, these shifts

Table 2 Characteristic ^{1}H chemical shifts of enamines **1a–7b** in DMSO and correlations to the conformation around the exocyclic Cα–Cε bond.[c]

Enamine	δ (^{1}H)/ppm H1	Hγ2	Hδ2	NOESY-based conformation
1a	6.17	1.75–1.45[a]	2.97	n. ass.[b]
1b	6.18	1.76	2.98	n. ass.[b]
2a	***5.27***	1.80–1.35[a]	3.07	n. det.
2b	***5.42***	1.65–1.35[a]	3.04	n.det.
3a	***5.26***	1.55	3.06	*sc-endo*
3b	***5.37***	1.50	3.02	*sc-endo*
4a	***5.20***	1.75–1.30[a]	3.11	n. det.
4b	***5.37***	1.65–1.35[a]	3.09	n. det.
5a	5.94	***0.01***	***2.37***	*sc-exo*
5b	6.06	***0.01***	***2.37***	*sc-exo*
6a	6.19	***0.34***	***2.33***	*sc-exo*
6b	6.29	***0.25***	***2.34***	*sc-exo*
7a	6.05	***0.30***	***2.23***	n. det.
7b	6.22	***0.25***	***2.27***	*sc-exo*

[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.

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**).

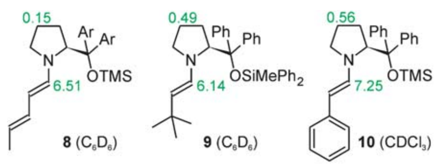
In addition, the possible solvent effects on the preferred population of these conformations were investigated (Table 3). As the detection of prolinol enamines was only successful in DMSO-d_6, these solvent studies were performed for only the diarylprolinol ether enamines, on the examples of **5b** and **7b**. The characteristic upfield-shifts of Hγ2/δ2 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 Cα–Cε bond of diarylprolinol ether enamines.

Altogether, our straightforward ^{1}H NMR screening method, backed by NOESY analyses, shows that the protection of the hydroxylic 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 (^{i}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 hydroxylic group of prolinols does not only have a significant impact on the stability of the corresponding enamines,[46] but also on the orientation of the bulky pyrrolidine α-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,[39] but also enables the interpretation of previous reported NMR data on comparable enamine species.[39b,41] Following our ^{1}H chemical shift screening criterion for Cα–Cε bond conformations, the enamines **8–10** (Scheme 3) are to be classified as *sc-exo* too, as upfield-shifted pyrrolidine resonances, but no significant upfield-shifts of H1, are observed.

Furthermore, our results provide the first broad experimental basis to clarify the recently presented conflicting results from theoretical calculations on the Cα–Cε 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,[39b] back the *sc-exo* conformation[39b,45] and reject the *sc-endo* conformation[41,43,44] 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.



Scheme 3 ^{1}H chemical shifts of diarylprolinol silyl ether enamines reported in the literature: **8** was observed *in situ* by Jørgensen *et al.*[41] and **9** and **10** were isolated and investigated in Seebach's group.[39b] (Note: H1 of **9** and **10** had obviously been mis-assigned by accident in the literature.)

Table 3 Characteristic ^{1}H chemical shifts of enamines **5b** and **7b** in different solvents and their correlations to the conformation around the exocyclic Cα–Cε bond.[a]

Enamine	Solvent	δ (^{1}H)/ppm H1	Hγ2	Hδ2	NOESY-based conformation
5b	DMSO-d_6	6.06	***0.01***	***2.37***	*sc-exo*
	MeCN-d_3	6.14	***0.08***	***2.43***	n. det.
	MeOH-d_4	6.10	***0.14***	***2.44***	n. det.
	$CDCl_3$	6.11	***0.10***	***2.48***	*sc-exo*
	PhMe-d_8	6.31	***0.22***	***2.53***	n. det.
7b	DMSO-d_6	6.22	***0.25***	***2.27***	*sc-exo*
	PhMe-d_8	6.12	***0.09***	***2.26***	n. det.

[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[72] 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 α-substituent around the Cα–Cε bond. Accordingly, the electrophilic attack of methyl vinyl ketone to the enamine occurs from the convex half-space opposite the "obese" diphenylmethoxymethyl substituent of **5b**. As previously pointed out,[39] 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[29,73–75] and the *O*-protecting group.[28,75–78] In addition, our finding of a stable *sc-exo* Cα–Cε 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.[79] All this data suggests that the *sc-exo*[45] conformation and not the *sc-endo*[43–45] 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 stereocontrol by diarylprolinol enamines, despite their rather limited applicability. Still, it is interesting to note that for prolinol enamines two different modes of stereocontrol 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[36] and, on the other hand, a directing function of the hydroxylic group *via* H-bonding interactions[35,37,38,79] to the electrophile on this "upper" face has been claimed. Interestingly, the *sc-endo* conformation around the Cα–Cε bond of diarylprolinol enamines that we observed in this study allows for both a H-bond from the hydroxylic 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[39] 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,[80] 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.[39] 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–Cε 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 noteable that upfield-shifted pyrrolidine protons have also been reported for diarylprolinol ether iminium salts,[39b,42] which, in combination with the crystallographic data,[39] 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 diarylmethanol substituent) can be straightforwardly screened for by means of NMR spectroscopy.

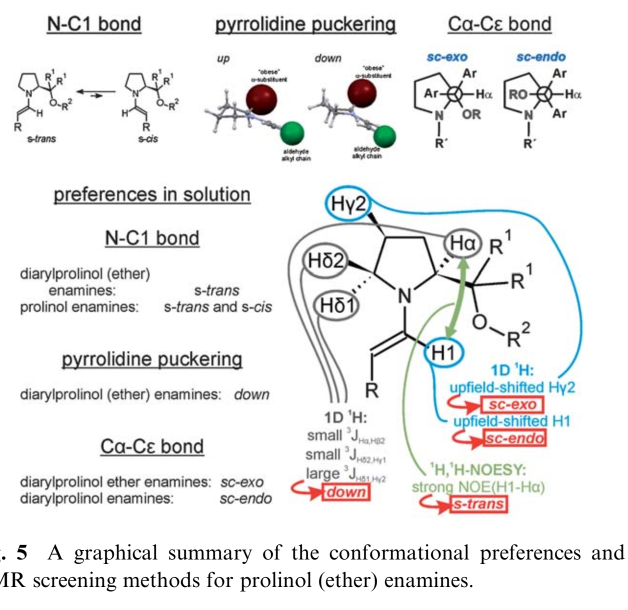


Fig. 5 A graphical summary of the conformational preferences and NMR screening methods for prolinol (ether) enamines.

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 α-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 CH/π interactions between the aliphatic hydrogen atoms of the pyrrolidine ring in the *down* conformation and an aromatic π system of the bulky pyrrolidine α-substituent. In addition, a rapid conformational screening method, based on ^{1}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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