Effect of the enamine pyramidalization direction on the reactivity of secondary amine organocatalysts

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Chiral secondary amines are valuable catalysts for reactions that proceed through an enamine intermediate. Here, we explored the importance of the pyramidalization direction of the enamine-N on the reactivity of chiral enamines with a combination of computational, NMR spectroscopic, and kinetic experiments. Studies with peptidic catalysts that bear cyclic amines with different ring sizes revealed that endo-pyramidalized enamines are significantly more reactive compared to exo-pyramidalized analogs. The results show that the pyramidalization direction can have a greater effect than n→π* orbital overlap on the reactivity of chiral enamines. The data enabled the development of a catalyst with higher reactivity compared to the parent catalyst.

Organocatalysts should be excellent for probing the reactivity of enamines – provided that the enamine intermediate is involved in the rate-determining step.

Herein we used peptidic catalysts bearing secondary amines with different ring sizes as tools to evaluate the effect of pyramidalization on the reactivity of enamines. We show that the pyramidalization direction can have a significant effect on the reactivity of Cα-substituted enamines. The results provided a guide that enabled the development of an organocatalyst with enhanced reactivity compared to the parent catalyst.

Introduction

Since the late 1990s, numerous chiral secondary amines have emerged as valuable catalysts for asymmetric reactions that proceed via an enamine intermediate (Scheme 1a).

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Herein we used peptidic catalysts bearing secondary amines with different ring sizes as tools to evaluate the effect of pyramidalization on the reactivity of enamines. We show that the pyramidalization direction can have a significant effect on the reactivity of Cα-substituted enamines. The results provided a guide that enabled the development of an organocatalyst with enhanced reactivity compared to the parent catalyst.

Results and discussion

The tripeptides H-Pro-Pro-Glu-NH₂ (1) and H-Pro-Pip-Glu-NH₂ (2, Pip = piperidine carboxylic acid) are highly reactive and stereoselective catalysts for conjugate addition reactions between aldehydes and nitroolefins. Mechanistic studies revealed that the enamine intermediate undergoes the rate and enantioselectivity-determining step and off-cycle intermediates.

Scheme 1  (a) Secondary amine catalyzed addition reaction of aldehydes to electrophiles. (b) Anti-attack of enamine. (c) Equilibrium between endo and exo pyramidalized enamines.
were not detected. Thus, this peptide-catalyzed reaction is a valid testing ground to probe for the effect of pyramidalization on enamine reactivity.

We reasoned that the conformational properties of differently sized cyclic secondary amines should result in enamines with different extents of pyramidalization and different endo/exo pyramidalization ratios of the enamine-N. Derivatives of peptide catalysts 1 and 2 with four- and six-membered N-terminal cyclic amines should therefore allow for probing the effect of pyramidalization.

**Computational analysis of enamines derived from cyclic amines with different ring sizes**

We started by computationally evaluating whether the pyramidalization of enamines formed by four-, five- and six-membered amines differs. Enamines derived from α-methyl substituted azetidine (3a), pyrrolidine (3), and piperidine (3b) were used as model compounds that are sufficiently small to allow for calculations within a reasonable time (Fig. 1). Conformational searches with MacroModel (OPLS3e force field, GB/SA solvent models for DMSO and CHCl₃) provided conformers in energy minima with geometries that were then optimized by DFT using the M06-2X-D3/6-31+G** level of theory. We used CHCl₃ for the calculations to be as close as possible to the solvent mixture used for the reactions as well as DMSO, a solvent in which enamines are sufficiently stable to be studied by NMR spectroscopy (vide infra). These calculations resulted in two conformers of 3a, five of 3, and four of 3b with a population of >3% according to the Boltzmann distribution. s-Trans enamines are the lowest energy conformers for all three compounds (Fig. 1).

The calculations predict significant differences regarding the degree and the direction of pyramidalization of the enamine-N of 3a, 3, and 3b: (a) the enamine-N is most planar in the pyrrolidine-derived enamine 3 (Δ = 0.23 Å) followed by that of the piperidine 3b (Δ = 0.30 Å) and the azetidine 3a (Δ = 0.42 Å) derivatives (Fig. 1). (b) The enamine-N in four-membered 3a is exclusively endo-pyramidal; for five-membered 3 a ratio of 83 : 17 in favour of endo is predicted and for six-membered 3b a ratio of 21 : 79 in favor of exo (Fig. 1). The predictions for 3a and 3 are in good agreement with crystal structures by Dunitz, Eschenmoser, Seebach, and List of proline- and azetidine-derived enamines or enaminoles in which the enamine-N is endo pyramidalized. In the structure of the piperidine derivative 3b, allylic strain enforces an axial position of the substituent at Cα and as a result the exo pyramidalization.

**NMR spectroscopic analysis of enamines derived from model compounds and catalysts bearing amines with different ring sizes**

To validate the computational findings we prepared enamines of butanal with the α-methylated cyclic amines (3a’, 3’, 3b’) and studied them by NMR spectroscopy (Fig. 2). In addition, we prepared and studied the enamines of analogs of peptidic catalyst 2 that bear four-, five-, and six-membered rings at the N-terminus (2a-En, 2-En, 2b-En; Fig. 2). Specifically, we measured ¹³C NMR spectra and monitored the chemical shift of the enamine carbon C(2) (Fig. 2). This chemical shift is a good measure for the electron density at C(2) and has been used by Mayr to evaluate the nucleophilicity of enamines. The more upfield shifted the carbon signal is, the stronger is the n → π⁺ donation and the more planar is the enamine. Since the enamines 2a-En and 2b-En proved too unstable to allow analysis in CDCl₃, we analysed them in d₆-DMSO, keeping in mind that the calculations had predicted comparable pyramidalization degrees and endo/exo ratios regardless of the solvent (Fig. 1). ¹³C NMR spectra showed as expected the highest upfield shift of C(2) for the five-membered enamine 2-En (98.6 ppm, Fig. 2). The C(2) of the piperidine-derived enamine 2b-En appears further upfield (100.9 ppm) than that of the azetidine-derived enamine 2a-En (104.7 ppm). The same trend was observed for the enamines 3a’ (101.9 ppm), 3’ (96.8 ppm), 3b’ (100.5 ppm) (Fig. 2) suggesting that the substituent at Cα does not affect the relative amount of n → π⁺ overlap to a significant extent. These chemical shift differences indicate a higher electron density, and thus greater planarity and higher nucleophilicity, at C(2) of the enamine of piperidine compared to that of azetidine. Thus, the NMR spectroscopic data corroborate the higher planarity of the Piper-compared to the Azε-derived enamines predicted by the calculations.

**Catalysis with secondary amines of different ring sizes**

Based on these findings enamines derived from pyrrolidines should react fastest. The comparison of the reactivity of enamines from azetidine versus piperidine will allow to
elucidate whether the degree of pyramidalization ($n \rightarrow \pi^*$ overlap and electron density at C(2)) or another factor such as the pyramidalization direction is more or equally as important for the reactivity of enamines of chiral amines: if the degree of pyramidalization ($\delta$) is key, piperidine derivatives should react faster than azetidine derivatives. In contrast, if enamines with an endo-pyramidalized N react faster than exo-pyramidalized enamines, azetidine derivatives should outcompete piperidine derivatives. To compare the importance of these two effects, we studied the catalytic properties of H-DPro-Pip-Glu-NH$_2$ 2 and its analogues with four- (Aze, 2a) and six-membered (Pip, 2b) cyclic amines at the N-terminal position. NMR spectra of these three peptides are similar, in particular with respect to the observed interresidue NOEs, suggesting that their secondary structures are comparable.† We used the conjugate addition of butanal to $\mathcal{E}$-nitrostyrene to compare their reactivity (Scheme 2a).** The reaction was performed under conditions where the reaction rate is not influenced by the aldehyde (0 order), and the reaction of the enamine intermediate with the nitroeloen is rate-determining (CHCl$_3$/PrOH 9 : 1, 3 equiv. of butanal, 15 mM in catalyst). 3 mol% of 2a, 2, and 2b were used to ensure detectable product formation for all three catalysts within hours. To ascertain that the enamine intermediate is involved in the rate-determining step (and not the formation of the enamine) in case of all three catalysts we determined the rate constant for the reactions catalysed by 2a and 2b. These studies showed that the reactions are, as previously found for 1,15 0 order in aldehyde at butanal concentrations >1.5 M, the concentration which was used to compare the reactivity of 2, 2a, and 2b.† The rate order of nitrosoyrene is under these conditions ~0.5 similarly to what was previously found for 1 and corroborating that the enamine is involved in the rate-determining step.††

Monitoring of the reactions in situ by infrared spectroscopy revealed significant reaction rate differences (Scheme 2b). After two hours, parent peptide 2 had converted the starting materials quantitatively into the conjugate addition product, which was obtained with high stereoselectivity (d.r. 35 : 1 (syn : anti), 97% ee, Scheme 2a and b, red). After the same time, only ~50% conversion was observed in the presence of 2a with the 4-membered Aze as reactive centre (Scheme 2b, blue). The reactivity of 2b with the 6-membered Pip was even lower, with less than 5% conversion after two hours (Scheme 2b, green). Both catalysts provided the product with slightly lower but still good stereoselectivity (2a: d.r. 30 : 1; 94% ee and 2b: d.r. 26 : 1; 92% ee, Scheme 2a). Notably, in case of peptide 2b the same product enantiomer formed indicating that the minor endo N-pyramidalized enamine reacted predominantly. Reaction of the exo N-pyramidalized enamine with the nitroeloen via an anti-attack, would provide a different stereoisomer.

These relative reactivity differences of the three catalysts are also reflected in the activation energies ($E_a$) that were derived from Arrhenius plots of initial rates at different temperatures (20, 30, 40, 50, and 60 °C) under otherwise identical reaction conditions (Scheme 2c). The parent peptide 2 has the lowest activation energy (6.7 ± 0.5 kcal mol$^{-1}$) followed by those of the four-membered N-terminal amine 2a (10.8 ± 1.2 kcal mol$^{-1}$) and the six-membered amine 2b (13.0 ± 0.8 kcal mol$^{-1}$).

These findings show that the five-membered Pro derivative 2, with the most planar and mainly endo pyramidalized enamine-N is most reactive. The four-membered Aze derivative 2a is significantly more reactive compared to the six-membered Pip derivative 2b. Combined with the computational and NMR spectroscopic data, these results are consistent with a greater importance of endo-pyramidalization than the degree of n → $\pi^*$ overlap for the reactivity of chiral enamines.

**Enhancing the reactivity of secondary amine catalysts**

The computational studies predicted an endo/exo pyramidalization ratio of 83 : 17 for the enamine formed by chiral 5-membered cyclic amines (Fig. 1, middle). The presented data suggests that pyrrolidine derivatives with a higher endo/exo ratio should be even more reactive. We reasoned that bicyclic all-cis-2,3-methanoproline should favor endo-pyramidalized enamines by “locking” the pseudorotation of the pyrrolidine ring of proline. Computational studies with MacroModel and DFT using the same procedure as for the calculations of 3a, 3, and 3b, indeed predict a >100 : 1 ratio of endo/exo pyramidalization for the methyl substituted 2,3-methanopyrrolidine 3c, with a degree of pyramidalization ($\delta$ = 0.26 Å, Fig. 3) that is comparable to that of the proline derivative 3 ($\delta$ = 0.23 Å, Fig. 3).† Hence, a methanoproline derived catalyst should be more reactive than the corresponding Pro analogue. We therefore prepared peptide 2c with an N-terminal 4,5-methanoproline residue and compared its catalytic properties to those of parent peptide 2 (Fig. 3). Peptide 2c is indeed more reactive than 2 and converted butanal and nitrosoyrene quantitatively within 30 min into the conjugate addition product, which was obtained with a d.r. of 30 : 1 and an enantioselectivity of 98% ee.
In summary, we have shown the importance of endo-pyramidalization for endowing enamines derived from z-substituted secondary amines with high reactivity. Exo-pyramidalized enamines react slower due to the steric hindrance between the incoming electrophile and the Cz-substituent. Thus, the pyramidalization direction of the enamine-N is, together with the extent of n→π* overlap, important for the reactivity of chiral enamines. These findings provide an additional design element for the development of catalytically active chiral secondary amines – one of the most utilized types of organocatalysts. The reactivity of chiral enamines is likely more complex and not only determined by n→π* overlap and the enamine-N pyramidalization direction. This study might therefore also inspire further research to unravel thus far overlooked contributors to enamine reactivity.

Author contributions

T. S. and H. W. conceived the project and designed the experiments. T. S. and J. S. M. performed the experiments. T. S. and H. W. wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

†† Additional rate-limiting step of the reaction (ref. 14).

§§ The TFA-salts of the peptides were used for ease in accessibility and since previous studies had shown, that the presence of TFA/NMM does not affect the performance of the peptidic catalysts 1 and 2, ref. 128 and c. Higher amounts of aldehyde led to the formation of homoolal products, which hindered the analysis. For analogous experiments with 1 mol% of the catalysts, see the ESI (chapter 5.2).

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