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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.

Introduction

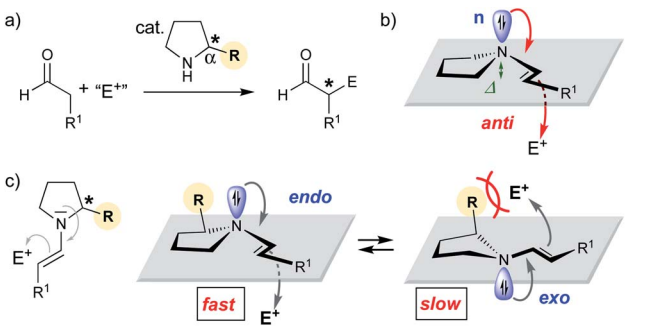
Since the late 1990s, numerous chiral secondary amines have emerged as valuable catalysts for asymmetric reactions that proceed *via* an enamine intermediate (Scheme 1a).[1] Proline and other α-substituted five-membered cyclic amines are the most commonly used catalysts for such aldol and related reactions.[1,2] Seminal work by Stork, Eschenmoser, and Seebach on stoichiometric reactions showed that enamines are most reactive when the enamine nitrogen is planar:[3–7] The higher the sp^2 character of the nitrogen is, the better is the donation of electron density from the non-bonding orbital (n) of N into the π* orbital of the enamine C–C double bond and the higher is the nucleophilicity (Scheme 1b).[3–10] The degree of sp^2 hybridization correlates with the degree of pyramidalization (*Δ*) of the enamine-N. Thus, the more planar, the better is the n→π* overlap and the more reactive is the enamine.[3–10] But is n→π* overlap really the only reason for reactivity differences of chiral enamines?

Stereoelectronic considerations require an attack of the enamine onto the electrophile *anti* to the n orbital (Scheme 1b).[11] We reasoned that the pyramidalization direction of the enamine-N should have a profound effect on the reactivity of enamines derived from chiral secondary amines. Enamines with an *endo* pyramidalization, where the n orbital is on the same side as the Cα-substituent should react faster than those with an *exo* pyramidalization due to the smaller steric hindrance for the incoming electrophile (Scheme 1c). 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.

Results and discussion

The tripeptides H-DPro-Pro-Glu-NH_2 (**1**) and H-DPro-Pip-Glu-NH_2 (**2**, Pip = piperidine carboxylic acid) are highly reactive and stereoselective catalysts for conjugate addition reactions between aldehydes and nitroolefins.[12,13] 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.

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were not detected.[14,15] 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 $CHCl_3$)[16,17] provided conformers in energy minima with geometries that were then optimized by DFT using the M06-2X-D3/6-31+G** level of theory.[18] We used $CHCl_3$ 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*-pyramidalized; 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 enaminones in which the enamine-N is *endo* pyramidalized.[4,19] In the structure of the piperidine derivative **3b**, allylic strain enforces an axial position of the substituent at Cα[20] and as a result the *exo* pyramidalization.

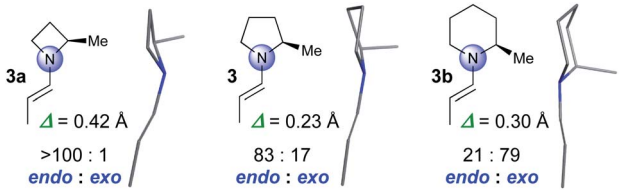


Fig. 1 Lowest energy structures of **3a**, **3** and **3b**. *Endo*/*exo* pyramidalization ratios and degree of pyramidalization (Δ) at N averaged over the absolute values of all calculated structures and weighted by their relative energies in $CHCl_3$. Values in DMSO are comparable (**3a**: Δ = 0.43, >100 : 1 *endo* : *exo*; **3**: Δ = 0.24, 84 : 16 *endo* : *exo*; **3b**: Δ = 0.34, 23 : 77 *endo* : *exo*).

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 ^{13}C 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.[9] 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 $CDCl_3$, we analysed them in d_6-DMSO, keeping in mind that the calculations had predicted comparable pyramidalization degrees and *endo*/*exo* ratios regardless of the solvent (Fig. 1). ^{13}C 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 Pip-compared to the Aze-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

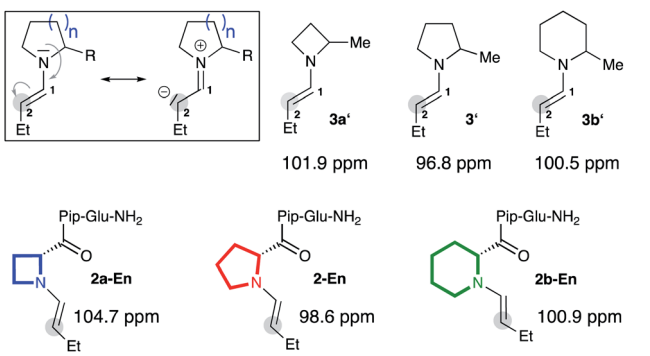
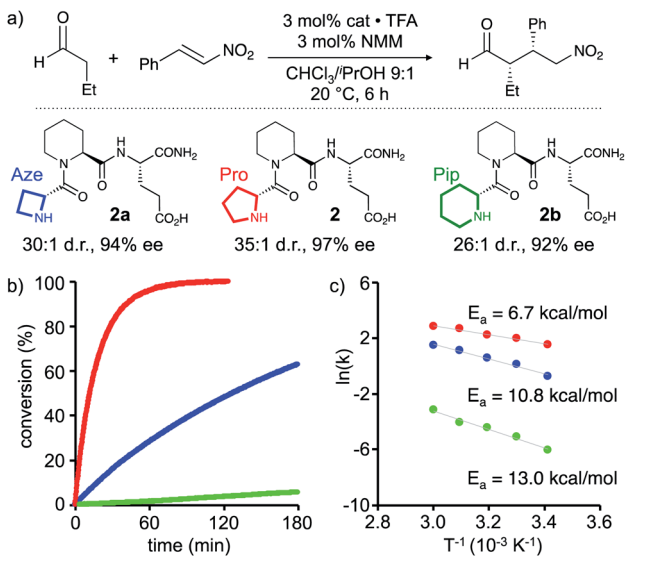


Fig. 2 ^{13}C NMR chemical shifts of C(2) of enamines derived from α-methyl azetidine (**3a′**), pyrrolidine (**3′**), piperidine (**3b′**) and catalysts **2a**, **2**, and **2b** in d_6-DMSO.

elucidate whether the degree of pyramidalization (n→π* 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 (Δ) 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-D-Pro-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 (*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 nitroolefin is rate-determining ($CHCl_3$/^{i}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 orders 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 nitrostyrene is under these conditions ~0.5 similarly to what was previously found for **1**[14] and corroborating that the enamine is involved in the rate-determining step.‡‡



Scheme 2 (a) Conjugate addition reaction of butanal to nitrostyrene catalyzed by **2a**, **2** and **2b**. (b) *In situ* IR monitoring of the formation of γ-nitroaldehyde, and (c) Arrhenius plot and activation energy of the peptide catalyzed reactions.

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 nitroolefin *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→π* 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 (Δ = 0.26 Å, Fig. 3) that is comparable to that of the proline derivative **3** (Δ = 0.23 Å, Fig. 3).[21] 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 nitrostyrene 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.

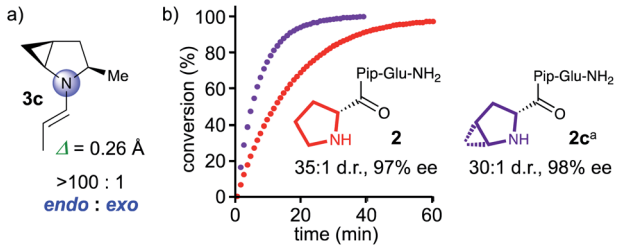


Fig. 3 (a) Calculated *endo*/*exo* pyramidalization ratio of enamine formed by α-methyl 4,5-methanopyrrolidine. (b) *In situ* IR monitoring of the conjugate addition reaction between butanal and nitrostyrene, catalyzed by **2** and **2c**. [a]Note, since D-methanoproline was not commercially available, the enantiomeric peptide was used and the enantiomeric product was obtained, see the ESI.†

Conclusions

In summary, we have shown the importance of *endo*-pyramidalization for endowing enamines derived from α-substituted secondary amines with high reactivity. *Exo*-pyramidalized enamines react slower due to the steric hindrance between the incoming electrophile and the Cα-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. developed the concept for the reactivity of enamines depending on their pyramidalization direction. J. S. M. developed catalyst **2c**. T. S., J. S. M. and H. W. wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

§ Note, for **3** and **3b**, conformers with the methyl group in equatorial and axial positions were found and conformers that differ in the ring pucker. For a complete listing of all structures and more details, see the ESI† (chapter 3).

¶ Comparable degrees of pyramidalization at N and the same trend of *endo*/*exo* pyramidalization ratios were obtained in calculations with enamines derived from pyrrolidinyl amides of Aze, Pro, and Pip; see the ESI† (chapter 3, p. S28) for details.

‖ We used butanal since prior studies with peptidic catalysts also used this aldehyde as a model compound (see, *e.g.* ref. 12–15) and enamines derived from butanal are less reactive compared to those made from propanal.

** Derivatives of peptide **2** were used since the *trans*/*cis* ratio of the DPro–Pip amide bond, which affects the reactivity of the tripeptidic catalysts, is higher compared to that of DPro–Pro of peptide **1**, see ref. 13. The kinetic experiments were also performed with analogues of peptide **1** bearing Aze and Pip, respectively, at the N-terminus and yielded the same conclusions, see the ESI† (chapter 5.3) for details.

†† NMR spectroscopic studies at −80 °C did not allow for monitoring *exo*- and *endo*-pyramidalized conformers of **3′** and **3b′** suggesting that the activation energy between them is <20 kcal mol^{-1} and rendering direct experimental evidence for the calculated *endo*/*exo* pyramidalization ratios difficult. (Note, a N-inversion barrier of ∼8 kcal mol^{-1} has been determined for *N*-methylpyrrolidine: J. M. Lehn, J. Wagner, *Tetrahedron*, 1970, **26**, 4227–4240.)

§§ 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. 12*b* and *c*. Higher amounts of aldehyde led to the formation of homoaldol products, which hindered the analysis. For analogous experiments with 1 mol% of the catalysts, see the ESI† (chapter 5.2).

‡‡ Note, the rate order of the nitroolefin is known to depend on the amount of water consistent with the hydrolysis of the iminium ion to the product as an additional rate-limiting step of the reaction (ref. 14).

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