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Author(s):

Möhler, Jasper Samuel Schnitzer, Tobias; Wennemers, Helma

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Amine Catalysis with Substrates Bearing N-Heterocyclic Moieties Enabled by Control over the Enamine Pyramidalization Direction

Jasper S. Möhler,[‡] Tobias Schnitzer,[‡] and Helma Wennemers*

Abstract: Stereoselective organocatalytic C–C bond formations that tolerate N-heterocycles are valuable since these moieties are common motifs in numerous chiral bioactive compounds. Such transformations are, however, challenging since N-heterocyclic moieties can interfere with the catalytic reaction. Here, we present a peptide that catalyzes conjugate addition reactions between aldehydes and nitroolefins bearing a broad range of different N-heterocyclic moieties with basic and/or H-bonding sites in excellent yields and stereoselectivities. Tuning of the pyramidalization direction of the enamine intermediate enabled the high stereoselectivity.

Introduction

Proline and related α -substituted chiral amines are powerful catalysts for stereoselective C–C bond forming reactions that proceed under mild conditions.^[1–3] Despite their widespread use, examples of such organocatalytic reactions with substrates bearing N-heterocyclic moieties are rare.^[1,2] Such functional groups are omnipresent in pharmaceuticals and agrochemicals with pyridines, pyrimidines, imidazoles, and pyrroles as prevalent representatives.^[4,5] Stereoselective transformations that proceed in the presence of these N-heterocycles are therefore important. Yet, these groups pose a major challenge to organocatalysts since their basic and/or H-bonding sites can interfere with the catalytic reaction by undesired interactions with the catalyst, the substrate, or reaction intermediates – thereby impairing stereoselectivity and yield (Scheme 1).^[6]

The conjugate addition reaction between aldehydes and nitroolefins is one of the most prominent organocatalytic reactions since the resulting γ -nitroaldehydes allow for further transformations into, e.g., 3,4-disubstituted pyrrolidines and γ -butyrolactams, compounds that are substructures of many biologically active compounds.^[2,4,7] Despite intense research on this reaction, examples with N-heterocyclic substituted γ -nitroaldehydes are seldom and mainly limited to 3-pyridyl moieties.^[8,9] All reported examples require either high catalyst loadings (5–20 mol%), the use of protecting groups on the N-heterocycle, and/or suffer from low enantio- and diastereoselectivities.^[8–10]

Scheme 1. a) Chiral amine catalyzed addition reactions that proceed via an enamine intermediate. b) Common heterocycles in therapeutics and their basic and H-bonding sites.

Peptide H-DPro-Pro-Glu-NH₂ (**1**) and related peptides are powerful organocatalysts for C–C bond formations and enabled access to γ -nitroaldehydes with aromatic and aliphatic substituents in excellent yields and stereoselectivities.^[11–15] Peptide **1** is so robust that functional groups such as esters and acetals are tolerated.^[11–14] Building on these findings we anticipated that an effective tripeptidic catalyst for conjugate addition reactions with substrates containing N-heterocyclic groups could be developed.^[10]

Herein we report highly stereoselective, organocatalytic conjugate addition reactions with nitroolefins bearing a broad variety of N-heterocyclic moieties with a carefully tailored peptidic catalyst. We show that a key factor for the high enantioselectivity is the formation of an *endo*-pyramidalized enamine intermediate.

Results and Discussion

We started by testing the catalytic performance of peptide **1** in the conjugate addition reaction between butanal and (*E*)-3-(2-nitrovinyl)pyridine. Using previously optimized conditions^[11,14] the γ -nitroaldehyde was obtained with good di- and enantioselectivity (d.r. 25:1, 89% ee; Scheme 2a, left). The stereoselectivity increased by using H-DPro-Pip-Glu-NH₂ (**2**, Pip = L-piperidine-2-carboxylic acid), a peptide with a higher *trans/cis* ratio of the tertiary amide bond (d.r. 35:1, 94% ee; Scheme 2a).^[14,15] While satisfactory, we deemed it necessary to develop a catalyst with an even better stereoselectivity for this model compound to meet the demands of substrates bearing different N-heterocycles.

Optimizing the stereoselectivity of chiral secondary amines by tailoring the enamine pyramidalization direction

Interference of N-heterocyclic substituents with the catalytic cycle is most severe if the conformation and reactivity of the intermediate that is involved in the rate- and stereoselectivity determining step is affected. We therefore reasoned that the

[a] J. S. Möhler, Dr. T. Schnitzer, Prof. H. Wennemers
Laboratory of Organic Chemistry, D-CHAB, ETH Zürich
Vladimir-Prelog-Weg 3, 8093 Zürich, Switzerland
Helma.Wennemers@org.chem.ethz.ch

[‡] These authors contributed equally to this work

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Scheme 2. a) Conjugate addition reaction between butanal and (*E*)-3-(2-nitrovinyl)pyridine catalyzed by peptides **1–5** (1 mol% cat-TFA, 1 mol% NMM, CHCl₃/PrOH 9:1, r.t., 2 h). Note, the enantiomers of **1** and **2** were used since only the (2*S*)-configured N-terminal Dhp derivative of **3** was commercially available; b) Effect of *endo/exo* pyramidalization of the enamine-N on the stereochemistry; c) Calculated *endo/exo* ratio of enamines **1a**, **3a–5a**. Data for **1a** and **4a** taken from ref. 19. Note, conversions, ee, and d.r. were determined from the crude mixture.

stereoselectivity could be improved by controlling the geometry of the enamine intermediate. Earlier mechanistic studies showed that the peptide-catalyzed reaction proceeds *via* an enamine intermediate that undergoes the rate and enantioselectivity determining C–C bond formation upon reaction with the electrophile.^[15–19] The conformation of the enamine has therefore an effect on the stereoselectivity of the reaction. Recently, we showed that enamines with an *endo*-pyramidalized N, in which the non-bonding orbital (*n*) is on the same side as the C α substituent of the catalyst react faster than enamines with an *exo*-pyramidalized N (Scheme 2b).^[19] Stereoelectronic considerations require an approach of the enamine onto an electrophile *anti* to the non-bonding orbital of the enamine-N.^[20,21] Thus, the pyramidalization direction of the enamine-N should also have a profound effect on the stereoselectivity: An *endo* pyramidalized enamine should approach the electrophile from the *Si* face, an *exo* pyramidalized enamine from the *Re* face, thus, yielding products with different stereochemistry (Scheme 2b). Control over the pyramidalization of the enamine-N should therefore increase the stereoselectivity of secondary amine catalysts. Somewhat surprisingly, the influence of the pyramidalization direction on the stereoselectivity of secondary amine catalysts has not been examined so far.

To explore the effect of the *endo/exo* ratio of the enamine-N on the stereoselectivity of the conjugate addition reaction, we started by calculating the lowest energy conformations of

enamines derived from α -methyl substituted pyrrolidine derivatives and propanal.^[22] Previous studies had shown that the enamine derived from α -methyl 4,5-methanopyrrolidine **4a** has a higher *endo/exo* ratio compared to that of α -methyl pyrrolidine **1a**.^[19] We reasoned that the *endo/exo* ratio of enamines formed by pyrrolidines with other alkyl substituents on the same face of the ring should be similar to that of **4a**. We therefore examined the enamine derived from all-*cis*-2-methyloctahydroindole (**5a**). In contrast, the constrained ring of α -methyl 3,4-didehydropyrrolidine should lead to an enamine (**3a**) with a lower *endo/exo* ratio. Conformational searches with MacroModel (OPLS3e force field, GB/SA solvent model for CHCl₃)^[23,24] followed by optimization of the obtained low energy conformers with DFT at the M06-2X-D3/6-31+G** level of theory^[25] supported these hypotheses.^[26] Enamine **3a** has the lowest *endo/exo* ratio (63:37), whereas a dominant *endo* pyramidalization at N was predicted for the enamines of the bicyclic pyrrolidine derivatives **4a** and **5a** (Scheme 2c). The predicted *endo/exo* ratio of the parent enamine of α -methylpyrrolidine **1a** is 83:17.

Next, we prepared analogues of the peptidic catalyst H-DPro-Pip-Glu-NH₂ **2** bearing the different pyrrolidine moieties at the N-terminus: H-Dhp-DPip-DGlu-NH₂ **3** (Dhp: (2*S*)-3,4-didehydropyrrolidine), H-MetPro-DPip-DGlu-NH₂ **4** (MetPro: (2*S*,4*S*,5*S*)-4,5-methanopyrrolidine), and H-Oic-DPip-DGlu-NH₂ **5** (Oic: (2*S*,3*aS*,7*aS*)-octahydro-1*H*-indole-2-carboxylic acid). Note, only the (2*S*)- but not the (2*R*)-configured derivative of Dhp was commercially available. We therefore prepared and tested the enantiomeric derivatives of catalyst **2**. One- and two-dimensional NMR spectra, including nuclear Overhauser effects, revealed the same secondary structure for all four catalysts.^[27] This finding suggests that differences in the stereoselectivity of catalysts **2–5** are not based on different secondary structures but their enamine geometries.

All peptides catalyzed the reaction between butanal and (*E*)-3-(2-nitrovinyl)pyridine but with different stereoselectivities (Scheme 2a). Peptide **3** with the N-terminal Dhp residue has a lower stereoselectivity (d.r. 30:1, 87% ee) compared to parent catalyst **2**. In contrast, catalysts **4** and **5** with the bicyclic derivatives provided the γ -nitroaldehyde with higher enantioselectivity (98% ee) than **2** and diastereoselectivities >25:1.^[28] These stereoselectivities reflect the trend of the predicted *endo/exo* ratios of the enamines.^[29] Since the diastereoselectivity of **5** with an Oic residue is greater (d.r. >50:1, *syn/anti*) compared to that of **4** with MetPro at the N-terminus, we used peptide **5** for all further studies.

We firstly probed the generality of the higher stereoselectivity of **5** compared to parent catalyst **2** by testing both catalysts in reactions between a range of different aldehydes and nitroolefins (Scheme 3). Nitroolefins without a N-heterocyclic moiety were used for these studies to ensure that differences in the stereoselectivities emerge from the different *endo/exo* ratios of the enamine of **2** and **5** and not from the N-heterocycle. All addition products were obtained with higher di- and enantioselectivity when catalyst **5** with the N-terminal Oic residue was used, corroborating the importance of the enamine geometry for reactions that proceed *via* an enamine intermediate. Noteworthy, all addition products were obtained with almost perfect stereoselectivities (d.r. >20:1, $\geq$ 98% ee).

Scheme 3. Comparison of the catalytic performance of **1** and **5** in conjugate addition reactions of aldehydes to nitroolefins (yields of the isolated product are >80%). 1 mol% of the peptide TFA salt and an equimolar amount of N-methylmorpholine (NMM) were used since previous studies showed that the presence of TFA/NMM does not affect the performance of the tripeptidic catalyst, ref. 17a. Data of catalyst **2** for products **6a–6c**, **6f** taken from ref. 14.

Scope of conjugate addition reactions with nitroolefins bearing N-heterocyclic moieties

Next, we evaluated the catalytic efficiency of peptide **5** for reactions with substrates bearing N-heterocyclic moieties (Schemes 4 and 5). We started with (*E*)-3-(2-nitrovinyl)pyridine, the nitroolefin that had been used before in organocatalytic reactions but necessitated the use of high catalyst loadings.^[8] Reassuringly, a range of different aldehydes including derivatives bearing sterically bulky substituents or functional groups such as esters and alkenes, reacted readily with (*E*)-3-(2-nitrovinyl)pyridine in the presence of as little as 0.5 mol% of peptide **5** and the products **7a–7i** were obtained in yields of 83%–95% and stereoselectivities of 95%–99% ee and 9:1–45:1 d.r. (Scheme 4). We continued by testing other nitroolefins bearing a variety of other six-membered (Scheme 4, **8a–10c**) and five-membered (Scheme 5) N-heterocyclic groups. These included pyridine, pyrimidine, oxazole, pyrrole, imidazole, and pyrazole substituents – moieties that are common in therapeutically active compounds^[4,5] but contain basic and/or H-bonding sites that could interfere with the catalytic reaction.

The nitroolefins with other six-membered N-heterocyclic groups such as methyl-substituted 3-pyridyl, 4-pyridyl, and 5-pyrimidinyl reacted with different aldehydes in the presence 0.5 mol% of **6** to the products **8a–8e**, **9a–9c**, and **10a–10c** with equally good to excellent yields and stereoselectivities (Scheme 4).

Also five-membered pyrazole and oxazole substituents did not interfere with the conjugate addition reaction and the γ -nitroaldehydes were isolated in high yields (79–99%) diastereoselectivities (15:1 – $\geq$ 50:1), and enantioselectivities of 98% or 99% ee (**11a–11f**, **12a**, and **12b**; Scheme 5). Further, conjugate addition products with pyrrole and imidazole moieties

Scheme 4. Scope of the conjugate addition reactions between aldehydes and nitroolefins bearing six-membered N-heterocycles with different basic and/or H-bonding sites. Yields of the isolated products, diastereoselectivities were determined by ¹H NMR spectroscopy of the isolated products, enantioselectivities were determined by chiral stationary phase SFC or HPLC analyses. ^a1 mol% of **5** was used.

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Scheme 5. Scope of the conjugate addition reactions between aldehydes and nitroolefins bearing five-membered N-heterocycles with different basic and/or H-bonding sites. Yields of the isolated products, diastereoselectivities were determined by ¹H NMR spectroscopy of the isolated products, enantioselectivities were determined by chiral stationary phase SFC or HPLC analyses. ^a2 mol% of **5** and CHCl₃/PrOH 1:1 were used.

bearing Boc or trityl protecting groups were obtained in high yields (85–98%) and stereoselectivities (**13a–13e**, **14a**, and **14b**; 4:1–≥50:1 d.r., 92–98% ee). Even nitroolefins bearing unprotected indole or pyrrole moieties provided the products at a slightly higher catalyst loading of 2 mol% in yields greater than 53% and good stereoselectivities (7:1–16:1 d.r., 86–92% ee; **16a–16c**, **17a**, and **17b**; Scheme 5). These results demonstrate how robust and tolerant peptidic catalyst **6** is to N-heterocyclic moieties. Basic

sites as well as H-bond donors and acceptors are readily accommodated.

We also evaluated whether the scope can be expanded to nitroolefins bearing saturated N-heterocycles, substrates that have similarly to most of the aromatic heterocyclic moieties so far not been explored (Scheme 6a). (*E*)-4-(*N*-Boc-piperidinyl)-nitroethylene reacted in the presence of peptide **5** (1 mol%) to product **17** in good yield (79%) and stereoselectivities (d.r. 25:1, 96% ee). Finally, we probed whether the conjugate addition reaction can be performed on a gram-scale and tested whether the obtained N-heterocycle containing product can be further derivatized (Scheme 6b). Reassuringly, 1.9 g of γ -nitroaldehyde **7a** were obtained at a similarly high level of stereoselectivity as on smaller scale. Noteworthy, this reaction proceeded when an excess of the nitroolefin was used in the presence of only 0.1 mol% of peptide **5**.^[14,16] Reductive amination of γ -nitroaldehydes is a convenient method to access chiral pyrrolidines that are common motifs in therapeutics.^[30] Treatment of **7a** with Zn in AcOH/water yielded pyrrolidine **18** in 87% yield and retained enantio- and diastereomeric enrichment (97% ee, d.r. 18:1).

Scheme 6. a) Synthesis of γ -nitroaldehyde **17** bearing a saturated N-heterocyclic substituent. b) Gram-scale synthesis of **7a** using 0.1 mol% of catalyst **5** and functionalization to pyrrolidine **18**; (I) 0.1 mol% NMM, CHCl₃/PrOH 9:1, r.t., 3 days.

Conclusions

In summary, we have introduced the H-Oic-DPip-DGlu-NH₂ as a powerful catalyst for conjugate addition reactions between aldehydes and nitroolefins bearing a variety of different N-heterocyclic moieties. The conformation of this peptidic catalyst was tailored to such an extent that it is sufficiently robust against substrates bearing non-innocent functional groups, including basic as well as H-bonding sites, unprotected and even saturated N-heterocycles. As a result, synthetically versatile γ -nitroaldehydes bearing a variety of different N-heterocyclic moieties were obtained in high yields and stereoselectivities at a catalyst loading of as little as 0.1–2 mol%. The results also showcase the value of *endo*-pyramidalized enamine intermediates for achieving high stereoselectivity, a finding that provides a guide for the optimization of chiral amine catalysts.

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Keywords: organocatalysis • N-heterocycles • peptides • conjugate addition reactions • enamines

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COMMUNICATION

Jasper S. Möhler,[‡] Tobias Schnitzer,[‡]
Helma Wennemers*

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**Amine Catalysis with Substrates
Bearing N-Heterocyclic Moieties
Enabled by Control over the Enamine
Pyramidalization Direction**

Accommodating N-heterocycles: The basic and H-bonding sites of N-heterocyclic moieties pose a major challenge to organocatalysis. A tailored peptide is introduced as a stereoselective catalyst for conjugate addition reactions with substrates bearing a broad range of N-heterocyclic moieties. Conformational studies highlight the importance of *endo*-pyramidalized enamines for high stereoselectivity.