Organocatalysis

Deutsche Ausgabe: DOI: 10.1002/ange.201602230
Internationale Ausgabe: DOI: 10.1002/anie.201602230

Peptide-Catalyzed Stereoselective Conjugate Addition Reactions of Aldehydes to Maleimide

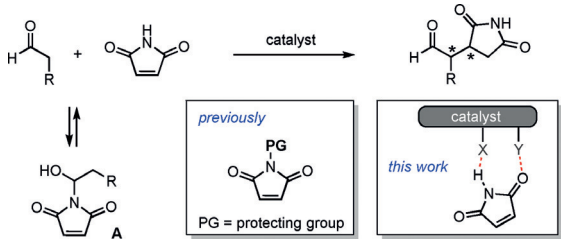
*Claudio E. Grünenfelder, Jessica K. Kisunzu, and Helma Wennemers**

Abstract: *The tripeptide H-D-Pro-Pro-Asn-NH_2 is presented as a catalyst for asymmetric conjugate addition reactions of aldehydes to maleimide. The peptidic catalyst promotes the reaction between various aldehydes and unprotected maleimide with high stereoselectivities and yields. The obtained products were readily derivatized to the corresponding pyrrolidines, lactams, lactones, and peptide-like compounds. ^{1}H NMR spectroscopic, crystallographic, and computational investigations provided insight into the conformational properties of H-D-Pro-Pro-Asn-NH_2 and revealed the importance of hydrogen bonding between the peptide and maleimide for catalyzing the stereoselective C–C bond formation.*

Succinimides are common motifs in natural products and versatile platforms for further transformations into, for example, pyrrolidines, lactams, or lactones, compounds that are widespread in therapeutically active compounds.[1] Effective methods for the stereoselective synthesis of succinimides are therefore valuable.[1–5] Stereoselective C–C bond formations between carbon-based nucleophiles and maleimides are attractive for obtaining succinimides.[1,3–5] Typically, *N*-protected maleimides are employed, presumably to circumvent potential side reactions arising from the nucleophilicity of unprotected maleimides.[3,4] This strategy requires an often cumbersome additional deprotection step to obtain the *N*-unfunctionalized succinimide.[4,6] The use of unprotected maleimide in conjugate additions with aldehydes would avoid this additional step, but has generally resulted in low product yields and/or stereoselectivities and required the use of comparatively high catalyst loadings of 10–20 mol %.[5] We envisioned that the hydrogen-bonding properties of peptide-based catalysts may allow us to overcome these limitations and provide controlled activation of unprotected maleimide towards the desired C–C bond formation.

Our group has previously introduced tripeptides of the general type H-Pro-Pro-Xaa (Xaa = any residue) as highly reactive and stereoselective catalysts for C–C bond formation reactions.[7–9] Tripeptides were developed that provide the products of aldol and conjugate addition reactions between aldehydes and nitroolefins in high yields as well as high enantio- and diastereoselectivities.[7–9] The modularity of the H-Pro-Pro-Xaa motif enabled tuning of the reactivity, stereoselectivity, and, remarkably, the chemoselectivity of the tripeptidic catalysts by structural modification. For example, while H-Pro-Pro-Asp-NH_2 is a powerful catalyst for aldol reactions,[7] the close analogue H-D-Pro-Pro-Glu-NH_2 (**1a**) catalyzes conjugate addition reactions of aldehydes to nitroolefins and products of the competing homoaldol reaction do not form.[8] This tunability of the steric and stereoelectronic properties had even enabled the development of tripeptidic catalysts for conjugate addition reactions of aldehydes to disubstituted nitroolefins where homoaldol reactions are typically the main pathway when other amine-based catalysts are employed.[9] We therefore envisioned that tripeptides of the type H-Pro-Pro-Xaa would also allow for the identification of a catalyst that accommodates the requirements for addition reactions of aldehydes to unprotected maleimides.

Herein, we present the peptide H-D-Pro-Pro-Asn-NH_2 as a catalyst for stereoselective 1,4-addition reactions of aldehydes to unprotected maleimide (Scheme 1). We show that hydrogen bonding of the catalyst to maleimide is key to overcoming unproductive side reactions and gearing the system towards the desired C–C bond formation. Furthermore, we show that the obtained succinimides can readily be converted into other synthetically useful compounds, such as pyrrolidines, lactams, and lactones.



Scheme 1. Conjugate addition of aldehydes to maleimide and the equilibrium between aldehydes and maleimide to form adduct **A**.

We started by exploring the reactivity of hydrocinnamaldehyde and maleimide and observed the reversible formation of an addition product **A** that can no longer engage in the desired conjugate addition reaction (Scheme 1).[10] This undesired side reaction can be prevented by using *N*-protected maleimides, which is likely the reason why previous studies focused on C–C bond formations with protected maleimides.[4] We speculated that the conjugate addition pathway could also be favored by coordination of unprotected maleimide to an appropriate catalyst. Since the pK_a values of maleimide (pK_a = 10.8)[11] and succinimide (pK_a = 14.6)[12] have been reported to differ by four units, we further hypothesized that the coordination of the formed succinimide

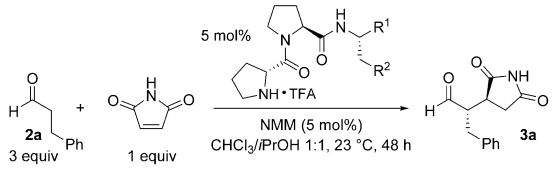
[*] C. E. Grünenfelder, Dr. J. K. Kisunzu, Prof. Dr. H. Wennemers
Laboratorium für Organische Chemie, ETH Zürich
Vladimir-Prelog-Weg 3, 8093 Zürich (Switzerland)
E-mail: Helma.Wennemers@org.chem.ethz.ch

Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201602230.

product to the catalyst would be sufficiently weaker compared to that of maleimide to allow for catalytic turnover.

Reassuringly, upon addition of tripeptides **1a–h** to mixtures of hydrocinnamaldehyde **2a** and maleimide the desired conjugate addition product **3a** formed (Table 1). Significant differences in the conversion of the starting materials into the product were observed depending on the functional groups of the C-terminal amino acid of the catalysts. Studies with H-DPro-Pro-Glu-NH_2 (**1a**) and related catalysts bearing carboxylic acid and amide moieties led to the desired product but with unsatisfactory conversion and significant amounts of products from homoaldol reactions.[13] Higher product formation was observed with peptides **1b** and **1c** bearing C-terminal amino acids with two amide moieties (Table 1, entries 2 and 3), suggesting that coordination between the catalyst and maleimide by hydrogen bonding rather than the presence of a proton donor is critical for enhancing the C–C bond-formation pathway. In experiments with peptide **1d** that lacks coordinating moieties, conjugate addition product **3a** hardly formed, which highlighted the importance of intermolecular interactions between the peptide and maleimide for catalysis (Table 1, entry 4). Further variations in the catalyst structure by replacing one of the amide moieties with non-coordinating functional groups (peptides **1e–h**, Table 1, entries 6–9; see also Table S1 in the Supporting Information) corroborated that H-DPro-Pro-Asn-NH_2 (**1c**) is the best catalyst with respect to reactivity and stereoselectivity. In addition, hardly any product from the homoaldol reaction of hydrocinnamaldehyde formed in the presence of peptide **1c**. Under optimized reaction parameters[14] with respect to, for example, solvent, stoichiometry, and concentration, the conjugate addition reaction proceeded quantitatively to succinimide **3a**, which was obtained with a diastereoselectivity of 88:12 and an enantioselectivity of 98% *ee* (Table 1, entry 5).

Table 1: Conjugate addition reactions of hydrocinnamaldehyde and maleimide catalyzed by peptides **1a–h**.



Entry	Cat.	R^1	R^2	Conc. [M]	Conv.[%][a]	d.r.[a]	*ee*[b] [%]
1[c]	**1a**	$CONH_2$	CH_2CO_2H	0.5	34	88:12	91
2[c]	**1b**	$CONH_2$	CH_2CONH_2	0.5	64	89:11	95
3[c]	**1c**	$CONH_2$	$CONH_2$	0.5	93	86:14	98
4[c]	**1d**	CO_2Me	Ph	0.5	< 5	n.d.[d]	n.d.[d]
5	**1c**	$CONH_2$	$CONH_2$	1.0	quant	88:12	98
6	**1e**	$CONH_2$	Me	1.0	50	88:12	81
7	**1f**	H	CH_2CONH_2	1.0	59	89:11	83
8	**1g**	$CONH_2$	Ph	1.0	45	91:9	88
9	**1h**	$CONH_2$	*i*Pr	1.0	54	92:8	88

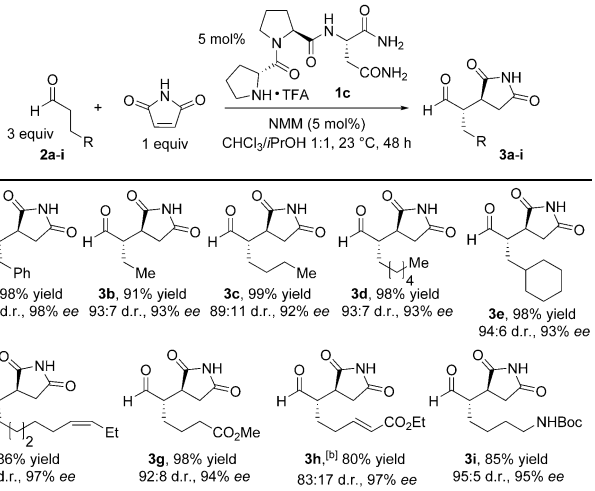
[a] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [b] Determined by HPLC on a chiral stationary phase. [c] A 9:1 ratio of $CHCl_3$/*i*PrOH was used. [d] not determined. NMM = *N*-methylmorpholine.

With the optimized reaction conditions in hand, we explored the scope of the peptide-catalyzed conjugate addition reaction and allowed a range of different aldehydes to react with maleimide in the presence of 5 mol% of peptide **1c** (Table 2). Aliphatic aldehydes readily reacted with maleimide and provided conjugate addition products **3a–3e** in high yields (91–99%) and stereoselectivities (92–98% *ee*, 88:12–94:6 d.r.). Aldehydes bearing ester, α,β-unsaturated ester, and even carbamate functionalities, which could potentially interfere by hydrogen bonding to the catalyst, were tolerated and yielded the corresponding products **3f–3i** with very good stereoselectivities (94–97% *ee*, 83:17–95:5 d.r.) albeit in slightly lower yields (80–98%).

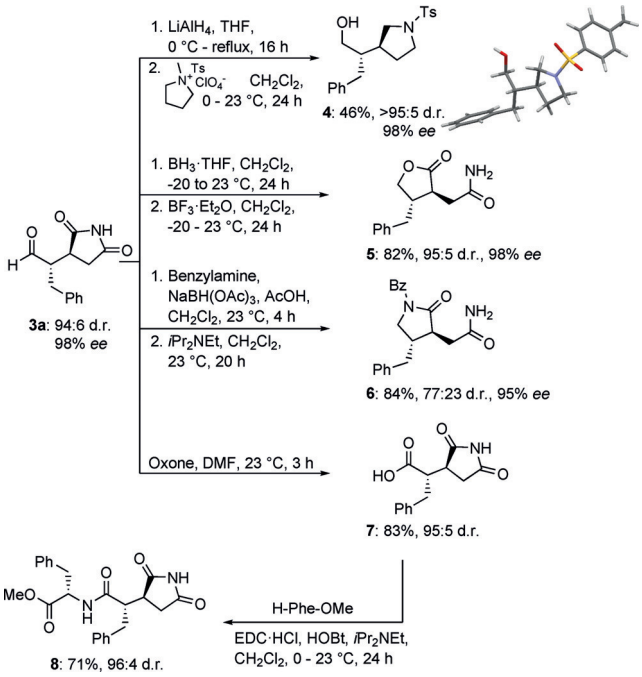
We then probed the synthetic utility of the conjugate addition products and used succinimide **3a** as a model compound. Reduction of the aldehyde and succinimide moieties yielded the corresponding pyrrolidine **4**, which crystallized after tosylation and allowed for the unambiguous assignment of the absolute and relative configuration of the stereogenic centers (Scheme 2, top).[15] Lactone **5** and lactam **6** were also obtained in high yields by straightforward two-step procedures that involved reduction of the aldehyde moiety, or that of an initially formed imine, followed by intramolecular ring opening of the succinimide moiety. Oxidation of the aldehyde moiety yielded acid **7** that could be easily used in a peptide coupling with, for example, L-phenylalanine methyl ester hydrochloride to yield **8** (Scheme 2). All of these reactions proceeded essentially with retention of diastereo- and enantioselectivity.

Next, we performed studies to gain an understanding of the role of the two amide moieties within peptide **1c** that had proven to be important for the catalytic efficiency. The experiments with analogues **1d–1h** had shown that both

Table 2: Scope of conjugate addition reactions between aldehydes and maleimide.[a]

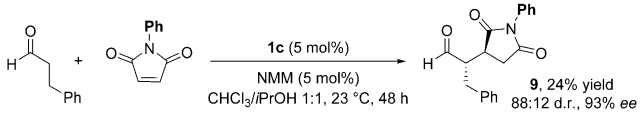


[a] Yields correspond to the isolated addition products as a mixture of diastereoisomers. The d.r. and *ee* values were determined by ^{1}H NMR spectroscopy and HPLC on a chiral stationary phase, respectively. [b] 10 mol% of catalyst were used.



Scheme 2. Derivatization of conjugate addition product **3a** and crystal structure of pyrrolidine **4**.[15] EDC·HCl = *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride; HOBt = *N*-hydroxybenzotriazole.

amides within **1c** are critical to obtain the product in high yields and stereoselectivities, which suggests that coordination between peptide **1c** and maleimide is key to the catalysis. This finding was further corroborated by reaction of *N*-protected phenylmaleimide that lacks the NH group as a H-bond donor. Reaction with hydrocinnamaldehyde in the presence of **1c** provided the product in lower yield (24%) and stereoselectivity (88:12 d.r., 93% *ee*, Scheme 3) compared to the identical reaction utilizing unprotected maleimide (Table 1, entry 5).



Scheme 3. Conjugate addition reaction of hydrocinnamaldehyde and *N*-phenylmaleimide catalyzed by peptide **1c**.

Since crystal structures can provide insight into the preferred conformation of peptides, we were pleased that the trifluoroacetic acid (TFA) salt of peptide **1c** crystallized from a mixture of $CHCl_3$, MeOH, and *n*-hexane (Figure 1a).[15] In the solid state, peptide **1c** adopts a β-turn structure within which the C-terminal amide NH moiety forms a H-bond with the CO group of the N-terminal proline. The side-chain amide of the asparagine (Asn) residue is coordinating a co-crystallized TFA molecule. This suggests that the C-terminal amide of the Asn residue plays a structural role whereas the side-chain amide moiety provides a binding site for the maleimide.

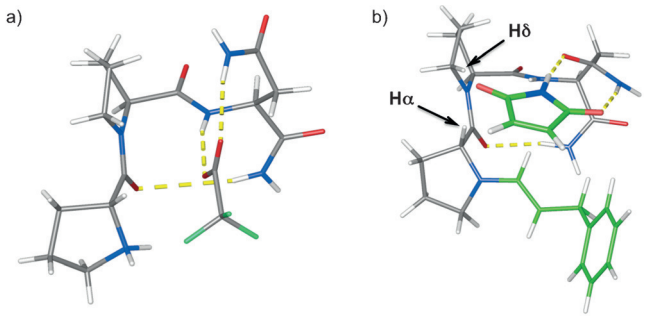


Figure 1. a) Crystal structure of the TFA salt of catalyst **1c**.[15] Atom colors in (a): C = gray; H = white; O = red; N = blue; F = green. b) Lowest energy structure of the catalyst enamine/maleimide complex calculated by MacroModel.[16] H-bonds indicated in yellow.

This dual role of the two amide moieties was supported by conformational searches using MacroModel 11.0 with the OPLS 2005 force field and the GB/SA model for chloroform.[16] The enamine derived from the crystal structure of **1c** and hydrocinnamaldehyde was used as a starting structure for coordination to maleimide. Within the resulting lowest energy conformation, the maleimide is coordinated to the asparagine side chain and allows for an attack of the enamine from below that supports the observed stereoselectivity (Figure 1b).

Finally, we probed the interaction between catalyst **1c** and maleimide in the solution phase and used ^{1}H NMR spectroscopy to monitor the interaction. N-terminally acetylated **1c** (Ac-D-Pro-Pro-Asn-NH_2; **1c-Ac**) was used for these studies in order to avoid interference by the secondary amine of the catalyst. Upon addition of maleimide to a solution of **1c-Ac**, pronounced downfield shifts of both the signals corresponding to the C-terminal and the side-chain amide-NH moieties of the Asn residue were detected.[14] In addition, significant changes in the chemical shifts of the signals corresponding to the H_α atom of the N-terminal Pro and one of the H_δ atoms of the middle Pro residue were detected. Both protons are in the vicinity of the maleimide in the calculated structure of the catalyst–maleimide complex (Figure 1b). Thus, the NMR spectroscopic studies support the proposed coordination mode between the peptidic catalyst **1c** and maleimide. Titration studies allowed for the determination of a binding affinity of $\Delta G = -1.1 \pm 0.2$ kcal mol^{-1}.[14,17]

In summary, we have developed an effective catalyst for conjugate addition reactions of aldehydes to unprotected maleimide. The resulting succinimides were obtained in high yields and stereoselectivities and further transformations to pyrrolidine, lactone, lactam, and peptide-like building blocks were straightforward. Coordination of the catalyst to maleimide by H-bonding proved to be key as revealed by studies with analogues as well as ^{1}H NMR spectroscopy and crystallography. The results highlight the value of peptidic catalysts[18] and their structural modularity, which allows for tuning of the chemoselectivity and thereby catalysis of reactions where undesired reaction pathways need to be avoided. Furthermore, these findings indicate that differential coordination, which is key for the substrate specificity of enzymes,[19] can also be implemented into peptidic catalysts.

Experimental Section

General procedure for the 1,4-addition reactions: The peptide (TFA salt, 20.0 μmol, 5 mol%) was added to a solution of *N*-methylmorpholine (NMM; 20.0 μmol, 5 mol%) in $CHCl_3$ and *i*PrOH (1:1, 0.4 mL) and the mixture was stirred for 5 min. Aldehyde (1.20 mmol, 3.0 equiv) and maleimide (0.40 mmol, 1.0 equiv) were added and the resulting solution was stirred at 23 °C for 48 h. The reaction mixture was directly purified by chromatography on silica gel using mixtures of ethyl acetate and hexane as eluents, which afforded the conjugate addition products **3a**–**3i**.

Acknowledgements

This work was supported by the Swiss National Science Foundation. J.K. is grateful to Novartis for a postdoctoral fellowship. We thank Dr. Nils Trapp and Michael Solar for recording the X-ray crystal structures.

Keywords: addition reactions · asymmetric catalysis · maleimide · organocatalysis · peptides

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 8571–8574
Angew. Chem. **2016**, *128*, 8713–8716

[1] For a recent review, see: P. Chauhan, J. Kaur, S. S. Chimni, *Chem. Asian J.* **2013**, *8*, 328–346.

[2] For examples of cycloadditions towards succinimides, see: a) O. Riant, H. B. Kagan, *Tetrahedron Lett.* **1989**, *30*, 7403–7406; b) D. Akalay, G. Dürner, M. W. Göbel, *Eur. J. Org. Chem.* **2008**, 2365–2368; c) C. Gioia, A. Hauville, L. Bernardi, F. Fini, A. Ricci, *Angew. Chem. Int. Ed.* **2008**, *47*, 9236–9239; *Angew. Chem.* **2008**, *120*, 9376–9379; d) J. Y. T. Soh, C. H. Tan, *J. Am. Chem. Soc.* **2009**, *131*, 6904–6905; e) S. Mukherjee, E. J. Corey, *Org. Lett.* **2010**, *12*, 632–635; f) L. Dell'Amico, A. Vega-Peñaloza, S. Cuadros, P. Melchiorre, *Angew. Chem. Int. Ed.* **2016**, *55*, 3313–3317; *Angew. Chem.* **2016**, *128*, 3374–3378; g) J. F. Bai, L. L. Wang, L. Peng, Y. L. Guo, J. N. Ming, F. Y. Wang, X. Y. Xu, L. X. Wang, *Eur. J. Org. Chem.* **2011**, 4472–4478; h) Y. Wang, L. Liu, T. Zhang, N. J. Zhong, D. Wang, Y. J. Chen, *J. Org. Chem.* **2012**, *77*, 4143–4147; i) Q. Y. Zhao, X. Y. Han, Y. Wei, M. Shi, Y. X. Lu, *Chem. Commun.* **2012**, *48*, 970–972; j) H. W. Zhao, Z. Yang, W. Meng, T. Tian, B. Li, X. Q. Song, X. Q. Chen, H. L. Pang, *Adv. Synth. Catal.* **2015**, *357*, 2492–2502.

[3] For metal-catalyzed C–C bond formations towards succinimides, see: a) R. Shintani, W. L. Duan, T. Hayashi, *J. Am. Chem. Soc.* **2006**, *128*, 5628–5629; b) E. Dardennes, S. Labano, N. S. Simpkins, C. Wilson, *Tetrahedron Lett.* **2007**, *48*, 6380–6383.

[4] For organocatalytic C–C bond formations towards succinimides, see: a) G. Bartoli, M. Bosco, A. Carlone, A. Cavalli, M. Locatelli, A. Mazzanti, P. Ricci, L. Sambri, P. Melchiorre, *Angew. Chem. Int. Ed.* **2006**, *45*, 4966–4970; *Angew. Chem.* **2006**, *118*, 5088–5092; b) G. L. Zhao, Y. M. Xu, H. Sundén, L. Eriksson, M. Sayah, A. Córdova, *Chem. Commun.* **2007**, 734–735; c) F. Xue, L. Liu, S. L. Zhang, W. H. Duan, W. Wang, *Chem. Eur. J.* **2010**, *16*, 7979–7982; d) S. Shirakawa, S. J. Terao, R. He, K. Maruoka, *Chem. Commun.* **2011**, *47*, 10557–10559; e) C. G. Kokotos, *Org. Lett.* **2013**, *15*, 2406–2409; f) S. Muramulla, J. A. Ma, J. C. G. Zhao, *Adv. Synth. Catal.* **2013**, *355*, 1260–1264; g) E. Gómez-Torres, D. A. Alonso, E. Gómez-Bengoa, C. Nájera, *Eur. J. Org. Chem.* **2013**, 1434–1440; h) G. Zhan, Q. He, X. Yuan, Y. C. Chen, *Org. Lett.* **2014**, *16*, 6000–6003.

[5] a) J. Flores-Ferrándiz, R. Chinchilla, *Tetrahedron: Asymmetry* **2014**, *25*, 1091–1094; b) A. Avila, R. Chinchilla, E. Gómez-Bengoa, C. Nájera, *Eur. J. Org. Chem.* **2013**, 5085–5092.

[6] D. G. Lonergan, G. Deslongchamps, *Tetrahedron* **1998**, *54*, 14041–14052.

[7] a) P. Krattiger, R. Kovasy, J. D. Revell, S. Ivan, H. Wennemers, *Org. Lett.* **2005**, *7*, 1101–1103; b) J. D. Revell, H. Wennemers, *Adv. Synth. Catal.* **2008**, *350*, 1046–1052; c) M. Messerer, H. Wennemers, *Synlett* **2011**, 499–502.

[8] a) M. Wiesner, J. D. Revell, S. Tonazzi, H. Wennemers, *J. Am. Chem. Soc.* **2008**, *130*, 5610–5611; b) M. Wiesner, M. Neuburger, H. Wennemers, *Chem. Eur. J.* **2009**, *15*, 10103–10109; c) Y. Arakawa, H. Wennemers, *ChemSusChem* **2013**, *6*, 242–245; d) F. Bächle, J. Duschmalé, C. Ebner, A. Pfaltz, H. Wennemers, *Angew. Chem. Int. Ed.* **2013**, *52*, 12619–12623; *Angew. Chem.* **2013**, *125*, 12851–12855; e) J. Duschmalé, S. Kohrt, H. Wennemers, *Chem. Commun.* **2014**, *50*, 8109–8112.

[9] a) J. Duschmalé, H. Wennemers, *Chem. Eur. J.* **2012**, *18*, 1111–1120; b) R. Kastl, H. Wennemers, *Angew. Chem. Int. Ed.* **2013**, *52*, 7228–7232; *Angew. Chem.* **2013**, *125*, 7369–7373.

[10] S. L. Vail, A. G. Pierce, *J. Org. Chem.* **1972**, *37*, 391–393. For example, when 3 equiv of hydrocinnamaldehyde were mixed with maleimide (1M), **A** formed in a ratio of about 1:1 with respect to maleimide.

[11] H. Falk, A. Leodolter, *Monatsh. Chem.* **1978**, *109*, 883–897.

[12] F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456–463.

[13] Diastereoisomeric peptides as well as other analogues of **1a**–**h** were also evaluated (Table S1).

[14] For details, see the Supporting Information.

[15] CCDC 1456934 (**4**) and 1456929 (TFA·**1c**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

[16] Schrödinger Release 2015-4: MacroModel, version 11.0, Schrödinger, LLC, New York, NY, **2015**. OPLS 2005 force field: D. Shivakumar, J. Williams, Y. Wu, W. Damm, J. Shelley, W. Sherman, *J. Chem. Theory Comput.* **2010**, *6*, 1509–1519. GB/SA model for chloroform: D. Qiu, P. S. Shenkin, F. P. Hollinger, W. C. Still, *J. Phys. Chem. A* **1997**, *101*, 3005–3014.

[17] Titration experiments with acetylated peptide **1h**, bearing a leucine instead of the Asn residue at the C-terminus, still showed changes in the chemical shifts corresponding to the C-terminal amide, but significantly smaller (or no) changes in the chemical shifts of the non-amide protons, which indicates a weaker binding affinity. Calculation of a reliable binding constant proved difficult and only allowed an estimate of $\Delta G < -1.0\ \text{kcal mol}^{-1}$.

[18] a) E. A. C. Davie, S. M. Mennen, Y. J. Xu, S. J. Miller, *Chem. Rev.* **2007**, *107*, 5759–5812; b) B. Lewandowski, H. Wennemers, *Curr. Opin. Chem. Biol.* **2014**, *22*, 40–46; c) H. Wennemers, *Chem. Commun.* **2011**, *47*, 12036–12041.

[19] J. R. Knowles, *Science* **1987**, *236*, 1252–1258.

Received: March 3, 2016
Published online: June 2, 2016

