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Thieme Chemistry Journals Awardees – Where Are They Now? A Stereoselective Tripeptide Catalyst for Conjugate Addition Reactions of Acetophenones to Dicyanoolefins

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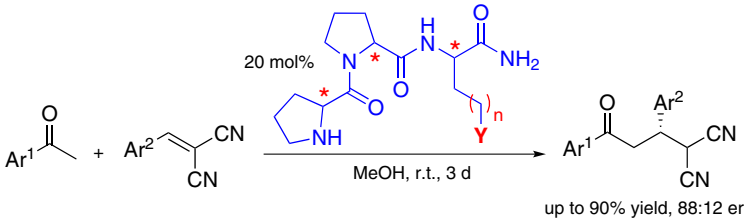

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Abstract Peptides of the type H-Pro-Pro-Xaa-NH_2 were evaluated as catalysts for conjugate addition reactions of acetophenones to cyanoolefins. Tripeptide H-D-Pro-Pro-Glu-NH_2 with a carboxylic acid moiety in the side chain of Xaa was identified as a catalyst that provides γ,γ-dicyanoacetophenones in yields of up to 90% and stereoselectivies of up to 88:12 er.

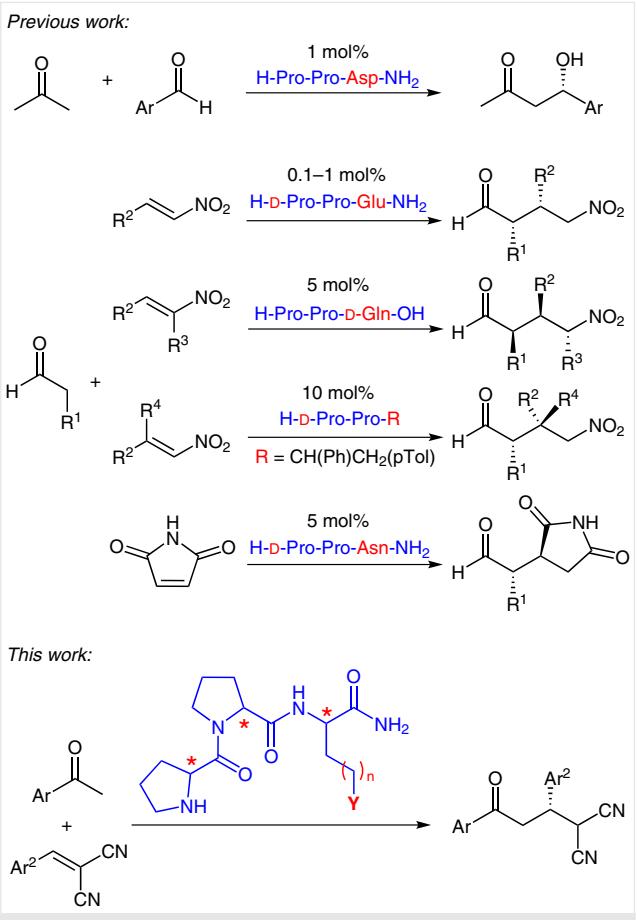
Key words peptides, organocatalysis, proline, nitriles, conjugate addition reactions

Nitriles are widespread in natural products[1] and versatile intermediates for the synthesis of amines, amides, and carbonyl compounds.[2] Hence, the introduction of cyano groups into organic molecules is important. Organocatalytic conjugate addition reactions of carbonyl compounds to α,β-unsaturated nitriles are an attractive means to access enantiomerically enriched nitrile-containing products. However, whereas numerous chiral amine-based catalysts have been developed that activate aldehydes and ketones by enamine formation for reactions with Michael acceptors (e.g., nitroolefins, acrylates, α,β-unsaturated carbonyl compounds),[3] examples of related addition reactions to cyanoolefins are rare.[4] Since pioneering studies by Enders[5] on stoichiometric addition reactions of SAMP- and RAMP-hydrazones to dicyanoolefins only a few catalytic reactions have been reported, which are typically part of cascade reactions.[4] One challenge arises from the weak interaction of cyanoolefins with hydrogen-bond donors, which renders substrate activation difficult.[6]

Herein we explored amine-based catalysts of the type Pro-Pro-Xaa bearing different functional groups in the side chain of the Xaa residue as catalysts for conjugate addition reactions between carbonyl compounds and cyanoolefins. We show that the tripeptide H-D-Pro-Pro-Glu-NH_2 catalyzes addition reactions between acetophenones and dicyanoolefins and provides γ,γ-dicyanoacetophenones with good yields and stereoselectivities.

Helma Wennemers studied chemistry at the Johann-Wolfgang-Goethe University in Frankfurt before moving to Columbia University, New York, where she received her Ph.D. degree for studies with W. Clark Still in 1996. Following postdoctoral studies at Nagoya University with Hisashi Yamamoto (1997–1998), she joined the faculty of Basel University as the Bachem-endowed Assistant Professor in 1999. She was promoted to Associate Professor (2004) at the University of Basel before moving to ETH Zurich in the fall of 2011 where she is Professor of Organic Chemistry. Her research focuses on the development of small molecules with functions that are fulfilled in nature by large macromolecules. She utilizes the power of organic synthesis to access functionalities that nature might have not had in the repertoire of building blocks. The focus is both on practical applications and an understanding of the properties on the molecular level. This scope includes the development of bioinspired asymmetric catalysts, functionalizable collagen, the controlled formation of metal nanoparticles as well as the use of molecular scaffolds for applications in supramolecular and biological chemistry (*e.g.*, cell-penetrating peptides, and tumor targeting). Helma is a fellow of ChemPubSoc Europe and the Royal Society of Chemistry and received several other recognitions for her research, including the Thieme Chemistry Journal Award (2001), Göring Visiting Professorship, University of Wisconsin–Madison (2004), Leonidas Zervas Award (2010), David Ginsburg Lectureship (2010), Holger Erdtman Lectureship (2010), Auer von Welsbach Lectureship (2011), Novartis Lectures [University of Columbia (2011), University of Wisconsin, Madison (2012), University of Illinois–Champaign (2015), University of Pennsylvania (2017)], European Journal of Organic Chemistry Lectureship (2014), Pedler Award (2016), JSPS Distinguished Lectureship (2016), and most recently Calvin Lectureship (University of California at Berkeley), Chemical Record Lectureship (2017), and the Inhoffen Medal (2017).

Peptidic catalysts of the Pro-Pro-Xaa-type are attractive for C–C bond formations that proceed via enamine activation of carbonyl compounds.[7–10] Highly stereoselective catalysts for aldol and conjugate addition reactions have been developed that require, compared to other secondary amine based catalysts, only low catalyst loadings for obtaining the products in high yields (Scheme 1).[7–11] Tailoring of the C-terminal amino acid (Xaa) and the absolute configuration of the stereogenic centers allowed for tuning of the reactivity, stereoselectivity, and notably also the chemoselectivity of the tripeptidic catalysts.[7–10] Even challenging substrates such as α,β- or β,β-disubstituted nitroolefins react in the presence of an appropriate tripeptidic catalyst to provide products with three consecutive stereogenic centers and a quaternary stereogenic center, respectively.[10] We therefore reasoned that Pro-Pro-Xaa-type catalysts provide a good testing ground for evaluating the effect of functional groups within secondary amine based catalysts on the reactivity of carbonyl compounds with cyanoolefins.

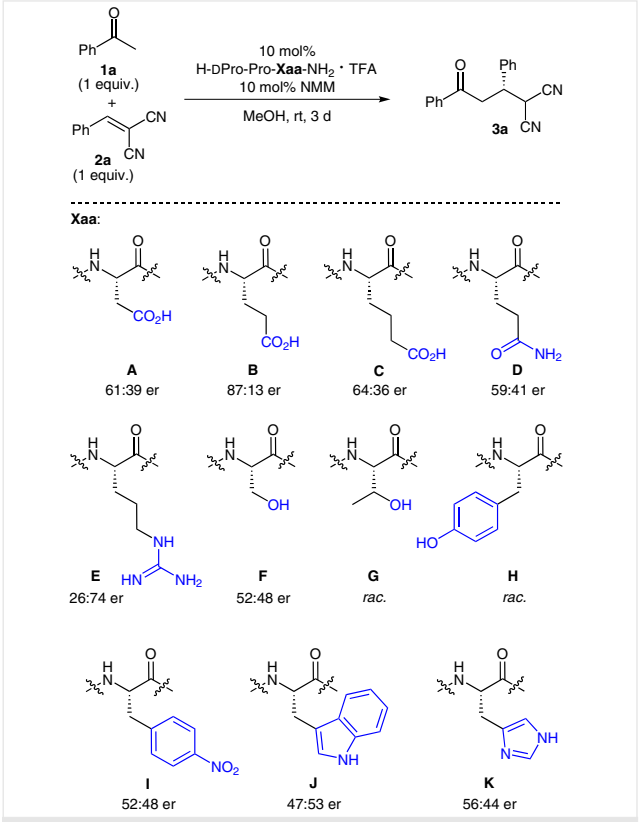


Scheme 1 Addition reactions catalyzed by Pro-Pro-Xaa-type peptides

Pro-Pro-Xaa catalysts with different residues in the Xaa position are easily accessible by solid-phase peptide synthesis. We therefore started by synthesizing peptides **A**–**K** that bear different proteinogenic and non-proteinogenic amino acids in the Xaa position (Scheme 2). The functional groups in the side chain of Xaa include proton donors, hydrogen-bond donors and acceptors, as well as aromatic moieties.

Initial trials to react monocyanoolefins (e.g., monocyanostyrene) with aldehydes in the presence of **A**–**K** showed little or no conversion. Conversely, reactions of aliphatic aldehydes and ketones (e.g., butanal, acetone, pentanone) with dicyanoolefins in the presence of the tripeptides provided products but in a fast and uncontrolled manner. We therefore turned to reactions between dicyanoolefins and acetophenones, which are particularly challenging substrates for catalysts that rely on the activation of carbonyl compounds by enamine formation.[12]

The reaction between acetophenone (**1a**) and dicyanostyrene (**2a**) served as a model reaction. The peptides were used as trifluoroacetic acid (TFA) salts and an equivalent amount of *N*-methylmorpholine (NMM) was added to liberate the secondary amine. These conditions were chosen for ease of synthesis of the peptides that were cleaved off the solid support by TFA, while keeping in mind that the presence of TFA can affect their catalytic performance.[13] The initial reactions were performed in methanol since all peptides were soluble in this solvent. Using equimolar amounts



Scheme 2 Testing of catalysts **A**–**K** in conjugate addition reactions between acetophenone **1a** and dicyanostyrene **2a**

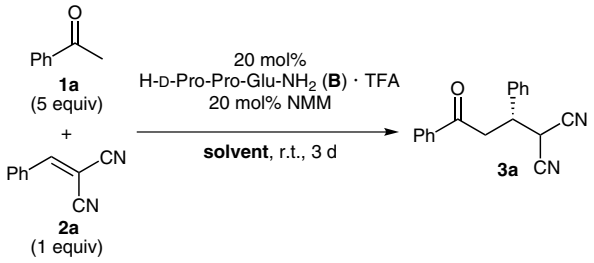
of acetophenone and dicyanostyrene and 10 mol% of the peptidic catalysts, the formation of the conjugate addition product **3a** was observed for all evaluated peptides, albeit typically with conversions of less than 20%. In light of the low reactivity of acetophenone, this poor conversion was not surprising and the performance of the catalysts was therefore mainly evaluated based on their enantioselectivity. In the presence of peptides bearing aliphatic or aromatic alcohol (**F**–**H**), aromatic (**H**–**K**), or amide (**D**) moieties γ,γ-dicyanoacetophenone (**3a**) was formed, but was essentially racemic (Scheme 2). Higher enantiomeric ratios were obtained when peptides with hydrogen-bond donors such as carboxylic acid (**A**–**C**) or guanidinium (**E**) moieties were used. H-D-Pro-Pro-Glu-NH_2 (**B**) exhibited the highest stereoselectivity and was therefore further investigated.

In previous studies the absolute configuration of catalysts of the type H-Pro-Pro-Xaa had been found to affect their reactivity and stereoselectivity.[7–10] We therefore prepared all diastereoisomers of **B** and evaluated their catalytic performance. Peptide H-Pro-D-Pro-Glu-NH_2 (14:86 er) performed equally well as **B** (87:13 er) but with opposite enantioselectivity. Such a switch in the enantioselectivity of diastereoisomeric catalysts had also been observed for other conjugate addition reactions catalyzed by H-Pro-Pro-Xaa peptides and is likely due to opposite turn conformations of the diastereoisomeric peptides.[8a] The other two diastereomers were less stereoselective (H-D-Pro-D-Pro-Glu-NH_2, 43:57 er and H-Pro-Pro-Glu-NH_2, 63:37 er) and also less reactive. We therefore continued the studies with H-D-Pro-Pro-Glu-NH_2 (**B**) and sought to optimize the reaction conditions further.[14]

Since the conformational properties of peptides and intermolecular interactions can be significantly affected by the solvent,[7b] we next performed a thorough testing of different solvents. To overcome the low conversions (<20%) observed in the initial trial, the catalyst loading was increased to 20 mol% and a fivefold excess of acetophenone was used. Reassuringly, the enantioselectivity of peptide **B** was maintained at 87:13 er under these conditions and the conversion increased to 72% (Table 1, entry 1). Testing of aromatic solvents, $CHCl_3$, THF, dioxane, EtOAc, MeCN, DMF, DMSO, and an ionic liquid (Table 1, entries 2–13) resulted in lower enantiomeric ratios compared to that obtained in MeOH and hardly any conversion of the starting materials into the product was observed. We therefore tested additional linear and branched alcohols (Table 1, entries 14–30) as solvents for the addition reaction.

In most of the alcoholic solvents conversions of more than 50% and enantiomeric ratios of higher than 80:20 were observed. In general, higher stereoselectivities were obtained in saturated linear alcohols (Table 1, entries 1, 14, 15, 17, 23, 24) compared to the corresponding branched al-

Table 1 Solvent Screening



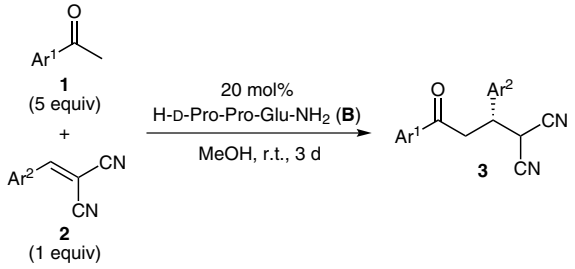
Entry	Solvent	er[a]	Conv. (%)[b]
1	MeOH	87:13	72
2[e]	benzene	56:44	<5
3[e]	anisole	67:33	<5
4[e]	nitrobenzene	68:32	<5
5[e]	C_6F_6	53:47	<5
6[e]	$CHCl_3$	75:25	<5
7	THF	44:55	<5
8	1,4-dioxane	69:30	5
9[e]	EtOAc	71:29	<5
10	MeCN	73:27	<5
11	DMF	62:38	n.d.[c]
12	DMSO	62:38	12
13	$BmimPF_6$	80:20	18
14	EtOH	86:14	83
15	*n*-PrOH	85:15	76
16	*i*-PrOH	83:17	76
17	*n*-BuOH	84:16	60
18[e]	*i*-BuOH	68:32	5
19	(*S*)-*s*-BuOH	76:24	18
20	(*R*)-*s*-BuOH	71:29	>95
21	*t*-BuOH	76:24	65
22	*t*-amyl alcohol	78:22	>95
23	*n*-HexOH	82:18	33
24	*n*-OctOH	80:20	18
25	TCE	–[d]	–[d]
26	TFE	–[d]	–[d]
27	HFIP	–[d]	–[d]
28	cyclohexanol	81:19	>95
29	propargyl alcohol	81:19	48
30	ethylene glycol	82:18	55

[a] Determined by chiral stationary phase SFC analysis.
[b] Estimated by ^1H NMR spectroscopy of the crude product, error ±5%.
[c] Decomposition of the starting material/product was observed.
[d] No product was formed.
[e] Poor solubility of the dicyanoolefin and/or peptide.

cohols with the same chain length (Table 1, entries 16, 18–22). In addition, the enantioselectivity was overall higher in alcohols with short linear aliphatic chains. This led us to hypothesize that solvents with OH acidity are beneficial for higher stereoselectivities. Yet, chlorinated and fluorinated alcohols were too acidic and suppressed the reaction (Table 1, entries 25–27). Also ethylene glycol, propargyl alcohol, and cyclohexanol as representatives of diols, unsaturated, and cyclic alcohols were tested but did not lead to improved stereoselectivities (Table 1, entries 28–30).

Next, we compared the performance of the TFA salt of **B** in the presence of NMM with that of peptide **B** where the TFA had been removed by ion-exchange chromatography. In the presence of this 'desalted' peptidic catalyst **B** full conversion to γ,γ-dicyanoacetophenone (**3a**) was observed with maintained stereoselectivity (88:21 er), and **3a** was isolated in a yield of 85% (Table 2, entry 1). These optimized conditions were then used for reactions between a couple of acetophenones and dicyanoolefins.[15] These experiments showed that peptidic catalyst **B** catalyzes reactions of dicyanoolefins bearing electron-deficient aromatic substituents (Table 2, entries 2 and 3) with product yields of up to 90% and enantiomeric ratios of up to 88:12. Dicyanoolefins bearing electron-rich moieties (Table 2, entries 4 and 5) and substituted acetophenone derivatives (Table 2, entries 6 and 7) were converted with good enantiomeric ratios of up to 87:13 but only poor conversions of less than 40%.

Table 2 Investigation of the Substrate Scope Using Optimized Conditions for the Michael Addition of Acetophenones **1** to Dicyanoolefins **2**



Entry	Ar^1	Ar^2	er[a]	Yield/Conv. (%)[b,c]
1	Ph	Ph	88:12	85
2	Ph	4-$O_2NC_6H_4$	87:13	90
3	Ph	4-ClC_6H_4	69:31	78
4	Ph	4-MeC_6H_4	87:13	(37)
5	Ph	4-$MeOC_6H_4$	87:13	(14)
6	4-$MeOC_6H_4$	Ph	87:13	(24)
7	3,5-$(CF_3)_2C_6H_4$	Ph	52:48	(<5)

[a] Determined by chiral stationary phase SFC analysis.
[b] Yield of the isolated products.
[c] Conversions listed in parentheses were estimated by ^1H NMR of the crude product, error ±5%. Products were only isolated in reactions with >50% conversion.

In summary, the testing of a collection of amine-based catalysts bearing different functional groups revealed the peptide H-D-Pro-Pro-Glu-NH_2 as a good catalyst for conjugate addition reactions of acetophenones to dicyanoolefins. The conjugate addition products formed in stereoselectivities of up to 88:12 er and 90% yield. The study showed that even challenging addition reaction donors such as acetophenone, with an intrinsically low reactivity, can be activated by peptidic catalysts to engage in conjugate addition reactions. Yet, the research also showed that the efficient activation of cyanoolefins remains a challenge.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588964.

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(14) Notably, this peptide is also a powerful catalyst for conjugate addition reactions between aldehydes and β-nitroolefins (ref. 8).

(15) The peptide catalyst **B** (0.2 equiv, 20 µmol) was dissolved in MeOH (400 µL). The acetophenone **1** (5 equiv, 500 µmol) and dicyanostyrene **2** (1 equiv, 100 µmol) were added, and the reaction mixture was stirred for 3 d. The reaction mixture was subjected to flash chromatography (hexane–EtOAc, 20:1 to 4:1) to isolate the product after removal of all volatiles under reduced pressure.

(*S*)-2-(3-Oxo-1,3-diphenylpropyl)malononitrile (Table 2, Entry 1)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01–7.92 (m, 2 H), 7.71–7.58 (m, 1 H), 7.51 (dd, *J* = 8.3, 6.9 Hz, 2 H), 7.41 (s, 3 H), 4.63 (d, *J* = 5.0 Hz, 1 H), 3.95 (dt, *J* = 8.2, 5.3 Hz, 1 H), 3.75–3.56 (m, 2 H).