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Small Peptide-Catalyzed Enantioselective Addition of Ketones to Nitroolefins

Yongmei Xu, Weibiao Zou, Henrik Sundén, Ismail Ibrahem, Armando Córdova*

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, 106 91 Stockholm, Sweden
Fax: (+46)-8-154-908, e-mail: acordova@organ.su.se

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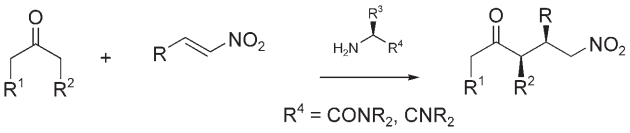
Abstract: The direct small peptide-catalyzed enantioselective Michael addition of ketones to nitroolefins is presented. Simple di- and tripeptides derived from alanine catalyze the asymmetric Michael additions with high stereoselectivity and furnish the corresponding Michael products in high yield with up to 68:1 dr and 98% ee. The study demonstrates that small, readily prepared peptides with increased structural complexity as compared to the parent amino acid mediate the asymmetric Michael reaction with superior reactivity and enantioselectivity.

Keywords: asymmetric catalysis; ketones; Michael reaction; nitroolefins; peptides

The Michael addition is a fundamental carbon-carbon bond-forming reaction in organic synthesis.[1] Therefore, chemists have developed several catalytic asymmetric protocols for this important reaction.[2] In recent years, an intense research effort has been made to find non-toxic chiral organic molecules as catalysts for enantioselective reactions.[3] For example, Miller[4] and Jacobsen[5] have employed catalytic peptides and peptide-like molecules as catalysts for asymmetric additions. Their structural diversity, availability and modularity could make them ideal asymmetric organocatalysts for a variety of transformations.[6] Proline[7] and *N*-terminal prolylpeptides[8] have been described as catalysts for the asymmetric Michael reaction. However, only moderate enantioselectivity is typically obtained. For example, proline and *N*-terminal prolyldipeptides catalyze the asymmetric formation of γ-nitroketones with 5–76% ee and 0–31% ee, respectively. Proline-derived derivatives have been proven to be more succesful for the asymmetric Michael reaction.[9–12] Recently, Alexakis,[13] Kotsuki,[14] Wang[15] and Hayashi[16] reported excellent highly enantioselective Michael conjugate additions that were catalyzed by chiral pyrrolidine-based catalysts. However, they are generally more complex and prepared in more steps than a simple amino acid or peptide catalysts. Herein, we present that simple dipeptides with a catalytic primary amine residue catalyze the direct asymmetric Michael addition of ketones to nitroolefins with high stereoselectivity and furnish the corresponding γ-nitro ketones with up to 68:1 dr and 98% ee.

Based on our research interest in asymmetric catalysis,[17] we recently found that acyclic aliphatic amino acids catalyze asymmetric intermolecular aldol reactions and Mannich reactions with high stereoselectivities.[18] The lessons from these studies made us interested in whether acyclic amino acids as well as small peptides derived from them could react with a ketone and form a catalytic chiral enamine, which could serve as a nucleophile in Michael additions to nitroolefins [Eq. (1)]. We expected that addition of a small excess of water would increase the efficiency and circumvent the need of adding an acidic additive. In addition, water would facilitate hydrogen bonding and proton transfer, which could plausibly improve the enantioselectivity of the Michael reaction.

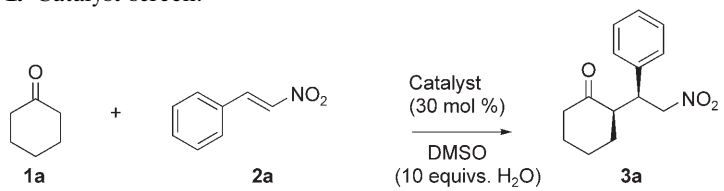


(1)

In an initial catalyst screen of the reaction between cyclohexanone **1a** and nitroolefin **2a** in wet DMSO, we found that acyclic primary amino acids catalyzed the asymmetric formation of Michael product (*R*, *S*)-**3a** in low yields (7–21%) and moderate to good ees (44–81%) (Table 1). The low yields were due to competing polymerization of the nitroolefin.

To our delight the *N*-terminal alanyldi- and tri-peptides were more efficient as compared to the primary amino acids at room temperature and furnished Michael product (*R*,*S*)-**3a** in higher yields (40–58%), diastereo-

Table 1. Catalyst screen.[a]



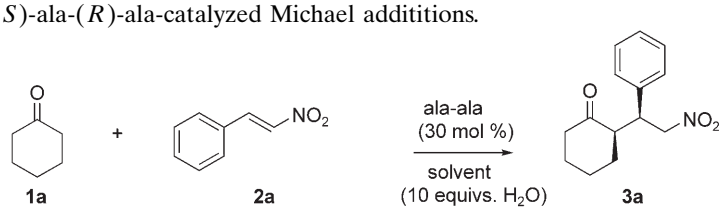
1a 2a 3a

Entry	Catalyst	Time [h]	Temp. [°C]	Yield [%][b]	dr[c]	ee [%][d]
1	ala	120	rt	21	6:1	81
2	asp	144	rt	12	2:1	44
3	Abu	120	rt	15	3:1	46
4	Nva	120	rt	17	3:1	52
5	ser	96	rt	21	3:1	72
6	alanine-tetrazole	60	rt	9	3:1	72
7	ala-ala	28	rt	55	12:1	84
8	ala-gly	28	rt	58	17:1	78
9	ala-phe	48	rt	40	12:1	85
10	ala-val	72	4	54[e]	22:1	89
11	ala-ala-OEt	216	rt	10	10:1	78
12	(*S*)-ala-(*R*)-ala	30	4	58[f]	24:1	94
13	val-val	240	4	13[e]	6:1	42
14	val-phe	120	4	18[e]	7:1	23
15	ser-ala	48	4	34[e]	10:1	74
16	ala-ala-ala	120	rt	37	14:1	84

[a] To a suspension of catalyst (30 mol %) in DMSO (1 mL), and H_2O (45 μL, 10 equivs.) were added ketone **1a** (0.75 mmol) and nitroolefin **2a** (0.25 mmol) and the resulting reaction mixture was stirred for the time and at the temperature shown in the table.
[b] Isolated yield of pure product **3a**.
[c] dr (*syn*:*anti*) as determined by NMR analyses.
[d] Determined by chiral-phase HPLC analyses.
[e] Reaction performed in a DMSO:NMP-1:1 mixture.
[f] Reaction performed in a DMSO:NMP-1:1 mixture with 45 mol % catalyst. NMP = *N*-methyl-2-pyrrolidinone, Abu = (2*S*)-2-aminobutyric acid, Nva = (*S*)-norvaline.

selectivities (6:1–24:1 dr) and ees (78–94%). Thus, increased structural complexity provides superior reactivity and stereoselectivity for the acyclic amino acid-catalyzed Michael reaction. In addition, the acid moiety of the dipeptide is important to achieve increased efficiency and asymmetric induction. For instance, the dipeptide ala-ala-OEt furnished **3a** in 10% yield with 10:1 dr (*syn*:*anti*) and 78% ee after 9 days, which is more than 20 times slower than ala-ala. We found that the dipeptides catalyze the Michael additions with best efficiency in NMP and DMSO. The highest efficiency and stereoselectivity was obtained when the ala-ala mediated reac-

Table 2. Examples of optimization experiments for the (*S*)-ala-(*S*)-ala-, (*S*)-ala-(*S*)-phe- and (*S*)-ala-(*R*)-ala-catalyzed Michael addititions.



1a **2a** **3a**

Entry	Solvent	Time [h]	Temp [°C]	Yield [%][b]	dr[c]	ee [%][d]
1	DMSO	28	rt	55	12:1	84
2	NMP	70	rt	47	21:1	87
3	DMSO	60	4	60	20:1	88
4	DMSO	66	4	55[e]	20:1[e]	85[e]
5	DMSO:NMP (1:1)	49	4	47	26:1	91
6	DMSO:NMP (1:1)	47	4	53[f]	17:1[f]	91[f]
7	DMSO:NMP (1:1)	50	4	60[g]	17:1[g]	91[g]
8	DMSO:NMP (4:1)	75	–20	58	68:1	93
9	DMSO:DMF (9:1)	240	–20	58	30:1	93
10	DMSO:$CHCl_3$ (1:1)	288	4	18	12:1	88
11	DMSO:NMP (1:1)	72	–20	62[h]	17:1[h]	97[h]

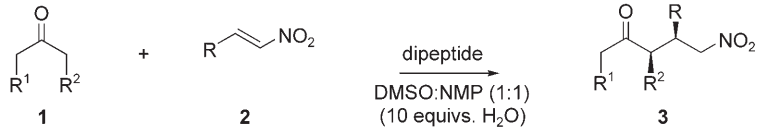
[a] To a suspension of catalyst (30 mol %) in solvent (1 mL), and H_2O (45 μL, 10 equivs.) were added ketone **1a** (0.75 mmol) and nitroolefin **2a** (0.25 mmol) and the resulting reaction mixture was stirred for the time and at the temperature shown in the table.
[b] Isolated yield of pure product **3a**.
[c] dr (*syn*:*anti*) as determined by NMR analyses.
[d] Determined by chiral-phase HPLC analyses.
[e] 5 equivs. H_2O.
[f] 20 equivs. H_2O.
[g] ala-phe used as the catalyst.
[h] (*S*)-ala-(*R*)-ala used as the catalyst.

tions were performed in a wet (10–20 equivs. H_2O) solvent mixture of DMSO:*N*-methyl-2-pyrrolidinone (NMP)-1:1 (Table 2).

The reaction was not efficient in $CHCl_3$ due to the low solubility of the dipeptide catalyst. In addition, decreasing the reaction temperature increased the stereoselectivity of the transformation. For example, (*S*)-ala-(*S*)-ala and (*S*)-ala-(*R*)-ala catalyzed the asymmetric formation of **3a** with up to 93% and 97% ee, respectively, at −20 °C (Table 2). The results demonstrated that changing the stereochemistry from (*S*) to (*R*) of the C-terminal amino acid of the dipeptide improved the enantioselectivity of the Michael addition. Encouraged by these results, we next probed the scope of the (*S*)-ala-(*S*)-ala- or (*S*)-ala-(*R*)-ala-catalyzed reaction with a set of ketones and nitroolefins (Table 3).

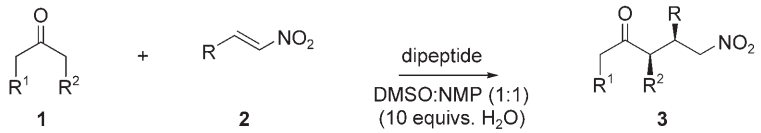
To our delight the dipeptides catalyzed the conjugate additions with cyclic ketones **1a**–**d** and **1f**, **g** as the donors with excellent enantioselectivity and furnished the Michael products **3a**–**g** and **3i**, **j** in good yield with 12:1–36:1 dr and 90–98% ee. For example, (*S*)-ala-(*R*)-ala mediated the asymmetric formation of **3b** in 79% yield with 22:1 dr and 98% ee. Having an electron-withdrawing group at the aromatic moiety of the nitroolefin increased the reactivity. Moreover, the dipeptides catalyze the Michael additions with protected dihydroxyacetone **1d**, which is an important donor in the *de novo* synthesis of carbohydrates,[19] to form 5-ni-

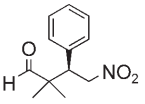
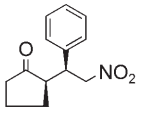
Table 3. The (*S*)-ala-(*S*)-ala- and (*S*)-ala-(*R*)-ala-catalyzed direct enantioselective Michael additions of ketones to nitroolefins.



Entry	Ketone	R	Product	Condition	Yield [%][b]	dr[c]	ee [%][d]
1	**1a**	Ph	**3a**	A	67	22:1	91
2	**1a**	Ph	**3a**	B	62	17:1	97
3	**1a**	Naphthyl	**3b**	B	79	22:1	98
4	**1a**	4-$MeOC_6H_4$	**3c**	B	76	20:1	92
5	**1a**	4-$NO_2C_6H_4$	**3d**	B[e]	68[e]	25:1[e]	94[e]
6	**1b**	Ph	**3e**	A	58	36:1	94
7	**1c**	Ph	**3f** / **3f'** (2:1)	A	69[f]	19:1[g]	92[h]
8	**1d**	Ph	**3g**	B	30	12:1	92
9	**1e**	Ph	**3h**	A	60 (23)[i]	1:2 (1:2)[i]	29 (40)[i]
10	**1f**	Ph	**3i**	B[i]	66	25:1	98
11	**1g**	Ph	**3j**	B	95	15:1	90

Table 3. (Continued).



Entry	Ketone	R	Product	Condition	Yield [%][b]	dr[c]	ee [%][d]
12	 **1h**	Ph	 **3k**	B[k]	57	-	58
13	 **1i**	Ph	 **3l**	A[l]	35	1:1	64 (79)[m]

[a] A = To a suspension of (*S*)-ala-(*S*)-ala (30 mol %) in DMSO:NMP (1:1) (1 mL), and H_2O (45 μL, 10 equivs.) were added ketone **1** (0.75 mmol) and nitroolefin **2** (0.25 mmol) and the resulting reaction mixture was stirred for 3 days at 4 °C. B = To a suspension of (*S*)-ala-(*R*)-ala (45 mol %) in DMSO:NMP (1:1) (1 mL), and H_2O (45 μL, 10 equivs.) were added ketone **1** (0.75 mmol) and nitroolefin **2** (0.25 mmol) and the resulting reaction mixture was stirred for 3 days at −20 °C.
[b] Isolated yield of pure product **3a**.
[c] dr (*syn*:*anti*) as determined by NMR analyses.
[d] Determined by chiral-phase HPLC analyses.
[e] Same conditions as B but the reaction time was 48 h.
[f] The combined yield of **3f** and **3f′** (2:1 ratio).
[g] dr for both **3f** and **3f′**.
[h] ee of **3f′**.
[i] Same conditions as A but reaction performed at −20 °C and run for 48 h.
[j] Same conditions as B but reaction performed at 4 °C and run for 48 h.
[k] Same conditions as B but 15 mol % catalyst.
[l] Same conditions as A but reaction perfotmed at room temperature.
[m] ee of the *anti*-diastereoisomer.

tro-5-deoxy-5-aryl-5-deoxypentoses such as **3g** with high diastereo- and enantioselectivity (12:1 dr and 92% ee). The ala-ala-catalyzed Michael addition with cyclopentanone gave the corresponding aldol product **3l** in good enantiomeric excess (79% ee). The primary amino acids and dipeptides were also able to utilize acyclic ketones and aldehydes as a donors. For example, ala-ala and (*S*)-ala-(*R*)-ala mediated the asymmetric formation of Michael products **3h** and **3k** with excellent regioselectivity and moderate enantioselectivity (40% ee) and in 58% yield with 58% ee, respectively.

We believe that the dipeptide-catalyzed asymmetric Michael reaction proceeds *via* a plausible catalytic enamine mechanism that is suggested in Figure 1. To explain the *syn*-diastereoselectivity and the absolute configuration observed, we propose transition state **I** based on Seebach's model for the dipeptide-catalyzed asymmetric Michael additions.[20] The acid moiety and the amide bond of the dipeptide plausibly assist in the stabilization of the transition state, which is improved by a small amount of water.

In summary, the direct, small peptide-catalyzed enantioselective Michael addition of ketones to nitroolefins is presented. Simple di- and tripeptides derived from alanine catalyze the asymmetric Michael additions with high chemo- and stereoselectivity and furnish the corresponding Michael products in high yield with up to 68:1 dr and 98% ee. The study demonstrates that simple peptides with increased complexity as compared to the parent amino acid mediate the Michael reaction with superior enantioselectivity and reactivity. Thus, readily prepared, highly modular peptides with a primary amine at the *N*-terminus should be considered in the design and tuning of novel inexpensive organocatalysts for the direct asymmetric Michael reaction. In addition, small peptides and their analogues are environmentally benign and non-toxic. Development of novel catalytic di- and tripeptide libraries and mechanistic studies are ongoing.

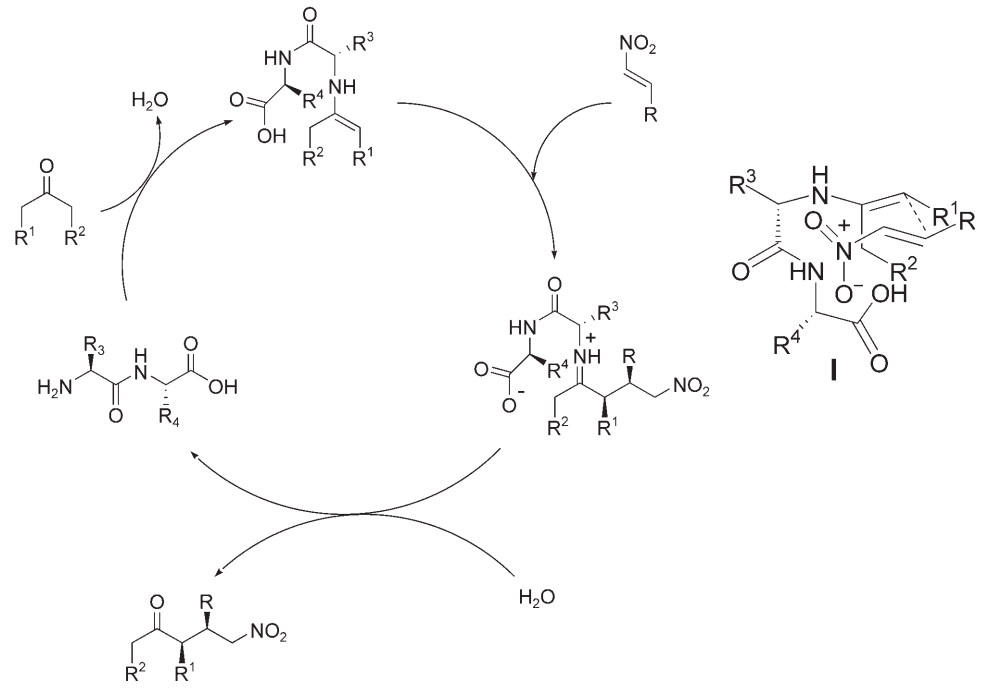


Figure 1. Plausible reaction mechanism and transition state **I** for the dipeptide-catalyzed asymmetric nitro-Michael reaction.

Experimental Section

General Procedure for the Conjugate Addition of a Ketone to a Nitroolefin

To a suspension of catalyst (30 mol %) in DMSO (0.5 mL), NMP (0.5 mL) and H_2O (45 μL, 10 equivs.) were added the relevant ketone (0.75 mmol) and nitroolefin (0.25 mmol). The resulting mixture was stirred for the time and temperature given in the tables. The reaction was quenched with brine and extracted with ethyl acetate (3×10 mL), the combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel/pentane:ethyl acetate = 10:1–4:1) to give the Michael products. The ee of the product was determined by chiral HPLC analysis. Relative (*syn*) and absolute configuration of the product was determined by comparison with the known ^{1}H NMR data and optical rotation values.

Acknowledgements

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