Dual Catalyst Control in the Chiral Diamine-Dipeptide-Catalyzed Asymmetric Michael Addition

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Abstract: By example of conjugate addition of 2-nitropropane to 2-cyclohexen-1-one, it is shown that the combination of H-Leu-His-OH and (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine as co-catalysts in a suitable ratio can lead to a new catalytic system for the C-C bond formation reactions. Although neither co-catalyst is sufficiently effective independently in terms of yield or enantioselectivity, their combination results in a drastic increase in yields (up to 86%) and absolute selectivities (up to 91% ee).

Key words: asymmetric organocatalysis, peptides, Michael additions, amines

The recent contributions by several groups in the field of asymmetric synthesis with amino acids[1] and short-chain peptides[2] as efficient chiral catalysts appear to be very interesting for chemists from academia as well as from industry.[3] Although amino acids such as proline and phenylalanine and derivatives have been used for a long time in enantioselective catalytic reactions,[4,5] the use of peptide-like enzyme mimics is a recent development and continues to receive growing interest for the C-C bond forming reactions.

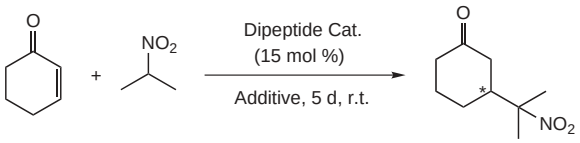
The Michael addition is one of the most frequently used C-C bond formation reactions in organic synthesis.[6] The development of asymmetric methodologies for this type of reaction has not only broadened its scope and applicability but has also provided insight into fundamental stereochemical aspects important to other carbon-carbon bond forming reactions such as Strecker synthesis, aldol and Diels–Alder reactions.

Proline[1c,e] and N-terminal prolyl di- and tripeptides[2e,g] have been reported recently as organic catalysts for asymmetric Michael additions.

To the best of our knowledge, no report is known of proline-free dipeptides catalyzing such reactions.

Herein we report a new catalytic system, based on dipeptides, for C-C bond formation reactions by example of asymmetric Michael additions.

The formation of C–C bonds by conjugate addition of appropriate carbanionic reagents to α,β-unsaturated carbonyl compounds is one of the most useful methods of remote functionalization in organic synthesis.[1c,6] Initially, we evaluated various dipeptides (H-Phe-His-OH, H-His-Phe-OH, H-Lys-Phe-OH, H-Leu-Arg-OH, H-Val-Arg-OH, H-Lys-Arg-OH, H-Lys-Tyr-OH, H-Lys-His-OH, H-His-Leu-OH, H-Leu-His-OH) as catalysts for the known asymmetric conjugate addition of 2-nitropropane to 2-cyclohexen-1-one (Scheme 1).



Scheme 1

Reactions were run at room temperature in DMSO or DMF under conditions employing 15 mol% of dipeptide and *trans*-2,5-dimethylpiperazine (**3**) as additive (Figure 1).[7] The peptides H-Leu-His-OH (**1**) and H-His-Leu-OH (**2**) were found to be the most promising dipeptide catalysts regarding enantioselectivities and yields. In DMSO much better yields (53%, 95%; entries 1 and 3, respectively), but overall lower enantioselectivities (29%, 26% ee, respectively) were observed in the presence of peptides **1** and **2**, relative to the results in less polar DMF (24%, 29% yields and 31%, 41% ee, entries 2 and 4 of Table 1, respectively). Peptide **1** in the absence of additives gave the *R*-product in DMSO with 13% yield and 42% ee (entry 5) and in DMF with 6% yield and 21% ee (entry 6).

In our initial studies, we have shown that even achiral *trans*-2,5-dimethylpiperazine alone resulted in product with 39.5% yield in DMSO (entry 7) and 5% yield in DMF (entry 8), and, therefore, influenced the enantiomeric excesses of the products when peptides were used as the catalysts[2g] (although the dominating influence on the enantioselectivities comes from the peptides). Accordingly, we assumed that the use of suitable chiral co-catalysts might improve further the enantiomeric excesses of dipeptide-catalyzed reactions and decided to perform our further experiments with commercially available chiral mono- and diamines **4**–**7** shown in the Figure 1.

Exchange of additive **3** for L-(–)-norephedrine (**4**) produced in DMSO as well as in DMF the *S*-enantiomer of the Michael product in much better yields [70–99%, but low to moderate enantioselectivities (3–31%), enties 9–12

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of Table 1]. Interestingly, the presence of additive **4** alone results in the *S*-product with 60% yield, 2% ee in DMSO and with 14% yield, 28% ee in DMF (entries 13, 14 of Table 1).

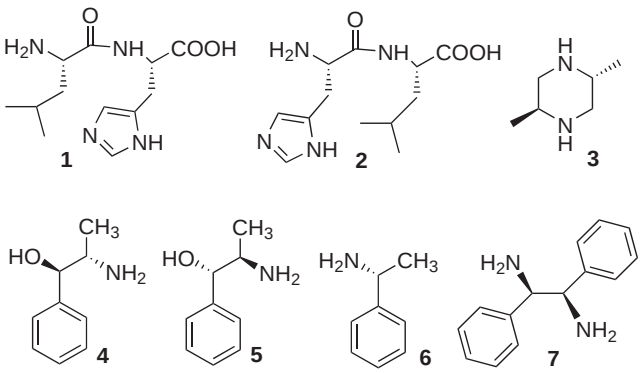

Figure 1

Table 1 Michael Addition Catalyzed by Dipeptides **1** and **2** in the Presence of Additives **3**–**7**

Entry	Dipeptide (15 mol%)	Additive (100 mol%)	Solvent	Yield (%)[a]	ee (%)[b]
1	**1**	**3**	DMSO	53	29 (*R*)
2	**1**	**3**	DMF	24	31 (*R*)
3	**2**	**3**	DMSO	95	26 (*R*)
4	**2**	**3**	DMF	29	41 (*R*)
5	**1**	–	DMSO	13	42 (*R*)
6	**1**	–	DMF	6	21 (*R*)
7	–	**3**	DMSO	39.5	–
8	–	**3**	DMF	5	–
9	**1**	**4**	DMSO	>99	3 (*S*)
10	**1**	**4**	DMF	77	31 (*S*)
11	**2**	**4**	DMSO	93	7 (*S*)
12	**2**	**4**	DMF	70	28 (*S*)
13	–	**4**	DMSO	60	2 (*S*)
14	–	**4**	DMF	14	28 (*S*)
15	**1**	**5**	DMF	79	32 (*R*)
16	–	**5**	DMF	21	32 (*R*)
17	**1**	**6**	DMF	74	45 (*S*)
18	**1**	**7**	DMF	**62**	**61 (*R*)**
19	**2**	**7**	DMF	34	49 (*R*)
20	–	**7**	DMF	12	45 (*R*)

[a] Isolated yields after chromatography.
[b] Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.

Also the use of D-(+)-norephedrine (**5**) in combination with dipeptide **1** in DMF provides the product with similar yield and enantioselectivity (79%, 32% ee, entry 15 vs 10, Table 1), but with opposite *R*-configuration, as expected. D-(+)-norephedrine alone gave *R*-product in 21% yield and 32% ee (entry 16).

Considering the results shown in entries 5, 9 and 13 (in DMSO) and also 6, 10, 14 (in DMF) one might conclude that even in the presence of dipeptides the influence on the enantioselectivities comes exclusively from the norephedrine. The variation of concentration of dipeptide **1** (0, 15, 30 mol%) and D-(+)-norephedrine (15, 30, 50, 100 mol%) and their different combinations did not lead to an increase in selectivity (being constant ca. 30% ee). However, the presence of both dipeptide and norephedrine drastically increases the yield of Michael product with respect to independently acting dipeptide or norephedrine and is much higher than the sum of its individual yields (entries 5, 9, 13 in DMSO; entries 6, 10, 14 in DMF with **4**, and entries 6, 15, 16 in DMF with **5**), which indicates the possibility of synergistic effects.

Next, we tested (*R*)-(+)-1-phenylethylamine (**6**) and (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine (**7**) as additives in DMF. Whereas the combination of **1** and co-catalyst **6** gives *S*-product with 74% yield and 45% ee (entry 17), the dipeptide **1**/co-catalyst **7** combination produces *R*-product with 62% yield and 61% ee (entry 18). The dipeptide **2** in combination with **7** gave under the same reaction conditions the product in only 34% yield and 49% ee (entry 19).

Interestingly, the use of **7** alone provides the *R*-product with 45% ee in 12% yield (entry 20).

These experiments show that the combination of dipeptide **1** with additive **7** provides a catalytic system that appears to be better than the sum of its parts (entries 6, 18, 20 of Table 1).

A matching pair of co-catalysts (**1**/**7**) was thus identified. Furthermore, several ratios of **1** and **7** have been tested (Table 2). To our surprise, the Michael addition in the presence of co-catalyst **7** and dipeptide **1** (30 mol% each) afforded a better result (86%, 75% ee, entry 3 of Table 2). Larger amounts of co-catalysts (entries 4, 5) provided better enantioselectivities (91% ee), but much lower yields (up to 41%).

In conclusion, we have demonstrated the first example of catalytic asymmetric conjugate addition in the presence of dipeptides H-Leu-His-OH, H-His-Leu-OH and achiral and chiral amines as co-catalysts. By example of conjugate addition of 2-nitropropane to 2-cyclohexen-1-one, we have shown that the combination of H-Leu-His-OH (**1**) and (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine (**7**) as co-catalysts in a suitable ratio can lead to a new catalytic system for the C–C bond formation reactions. Further investigations, involving mechanistic studies and optimization of the system, are in progress.

Table 2 Michael Addition Catalyzed by Dipeptide **1** in the Presence of (1*R*,2*R*)-(+)-1,2-Diphenylethylenediamine **7** as Additive (in DMF)

Entry	**1** (mol%)	**7** (mol%)	Yield (%)[a]	ee (%, *R*)[b]
1	15	30	21	42
2	15	100	62	61
3	**30**	**30**	**86**	**75**
4	50	100	41	91
5	100	100	39	91

[a] Isolated yields after chromatography.
[b] Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.

In addition we expect the further improved catalytic system to become useful for a variety of other C–C, C–N, C–S bond formation reactions and some other important transformations.

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(7) **General Procedure for the Michael Reaction:** 2-Nitropropane (0.63 mmol) was added to a stirred solution of 2-cyclohexen-1-one (0.50 mmol), additive (0.50 mmol) and peptide catalyst (15 mol%) in pre-dried solvent (DMF or DMSO, 4 mL), and the reaction mixture was stirred at r.t. for 5 d. The solvent was evaporated and the residue was dissolved in $CHCl_3$ and washed with diluted aq HCl (3%). The organic layer was dried with Na_2SO_4 and filtered, and the solvents were evaporated. The residues were purified by column chromatography on SiO_2 (hexane–EtOAc) to afford the desired product. The ee of the product was determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material: *n*-hexan–2-propanol = 80:20, flow rate 1 mL/min, λ = 210 nm: t_{R1} = 28.44 min, t_{R2} = 30.31 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.48–2.34 (m, 3 H), 2.31–2.21 (m, 1 H), 2.19–2.08 (m, 2 H), 1.85–1.76 (m, 1 H), 1.71–1.53 (m, 1 H), 1.58 (s, 3 H), 1.57 (s, 3 H), 1.48–1.34 (m, 1 H) ppm. ^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 208.9 (C=O), 90.6 ($C_{quat.}$), 46.5 (CH), 42.6 (CH_2), 40.7 (CH_2), 25.9 (CH_2), 24.3 (CH_2), 23.3 (CH_3), 22.5 (CH_3) ppm. ESI-MS (positive ion): *m/z* = 208.1 $[M + Na]^+$.