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(*S*)-Histidine-based dipeptides as organic catalysts for direct asymmetric aldol reactions

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Abstract—The structure/activity relationships for some (*S*)-histidine-based dipeptide catalysts in direct aldol reactions have been examined. The reactivities and stereoselectivities are shown to be dependent upon the intramolecular cooperation of side-chain functional groups and the presence of a suitable combination and sequence of amino acids. Good yields (up to 96%) and enantioselectivities (up to 76% ee) were obtained with electron-deficient aromatic aldehydes in the presence of H-Leu-His-OH. The influence of different chiral and achiral co-catalysts on the reaction rates, yields and enantioselectivities has also been evaluated. Significant increases in the acceleration of the reaction, most remarkable for achiral *trans*-2,5-dimethylpiperazine as co-catalyst and the improved yields, were demonstrated.

1. Introduction

The use of short peptides as asymmetric organic catalysts, pioneered by Inoue et al.[1–3] and Lipton et al.,[4] continues to receive growing interest for different important transformations[5–7] such as enantioselective conjugate additions,[8–10] asymmetric acylation reactions,[11] enantioselective phosphorylation,[12] Strecker synthesis,[13,14] Baylis–Hillman reactions[15] and enantioselective direct aldol reactions.[16–20]

The linear and cyclic dipeptides containing (*S*)-histidine, initially discovered by Inoue et al., have successfully been used for the asymmetric synthesis of cyanohydrins.[1–3]

However, no further attempts to apply Inoue's histidine-based dipeptide catalysts to other C–C bond formation reactions are known in the literature. This prompted our present study.

We became interested in extending the application of (*S*)-histidine-based dipeptide catalysts to other carbon–carbon bond forming reactions. We have recently reported asymmetric Michael additions catalyzed by linear dipeptides H-His-Leu-OH and H-Leu-His-OH.[21] Herein, we report the catalysis of an asymmetric direct aldol reaction (initially reported by List et al.[22] and Barbas et al.[23]), with some synthetic (*S*)-histidine-based dipeptides.

2. Results and discussion

Initially, we evaluated some dipeptides as catalysts for the known model reaction of acetone with 4-nitrobenzaldehyde (Table 1). Reactions were run at room temperature in DMSO under conditions employing 0.3 equiv of dipeptide relative to substrate and were allowed to proceed until completion.

Over the course of our studies, it was found that dipeptides with amino acids containing both one basic and one neutral residue are generally better suited to produce good conversions when compared to dipeptides of amino acids with other combinations of functionalities (Table 1, entries 1, 2, 4 and 6 vs entries 3 and 5).

The reactivities and stereoselectivities seem to be dependent upon the intramolecular cooperation of side-chain functional groups and the presence of a suitable combination and sequence of amino acids. Thus, H-His-Leu-OH, which has the reversed sequence of amino acid residues, is much less stereoselective (86%, 22% ee, entry

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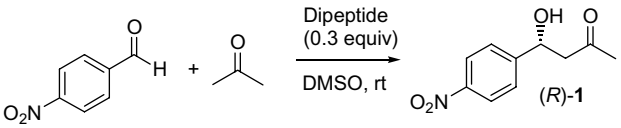
Table 1. Dipeptides tested as catalysts for the asymmetric aldol reaction of acetone with 4-nitrobenzaldehyde



Entry	Dipeptide	Reaction time (days)	Conv. (%)[a]	Reduced rates (%/h)[b]	Yield (%)[a]	ee (%)[c]
1	H-Phe-His-OH	8	92	0.48	79	27
2	H-His-Phe–OH	3	87	1.21	77	40
3	H-Leu-Phe-OH	8	17	0.09	11	67
4	**H-Leu-His-OH**	10	**96**	**0.40**	**87**	**71**
5	H-Lys-His-OH	10	13	0.05	11	26
6	H-His-Leu-OH	3	94	1.31	86	22
7	*cyclo*-[(*S*)-Leu-(*S*)-His]	10	31	0.13	24	3
8	H-Leu-His-OMe	10	92	0.38	81	60
9	Z-Leu-His-OMe	10	45	0.19	31	20

[a] Determined by ^{1}H NMR of crude mixture after completion of the reaction.
[b] [Conv. (%)]/[reaction time (h)].
[c] Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.

6) than H-Leu-His-OH (87%, 71% ee, entry 4), but shows a higher conversion rate (Table 1, reduced rates: 1.31 with H-His-Leu-OH vs 0.40 with H-Leu-His-OH). In the case of H-His-Phe-OH and H-Phe-His-OH, we observed similar results in terms of reaction rates, but reversed behaviour with respect to enantioselectivities regarding the position of the basic residue: H-His-Phe-OH catalyzes the reaction faster and gives better ees (Table 1, reduced rate 1.21; 77%, 40% ee, entry 2) than H-Phe-His-OH (Table 1, reduced rate 0.48; 79%, 27% ee, entry 1). We suppose that those shifts in selectivity observed for catalysis by these peptides may have been caused by a combination of steric and structural influences.

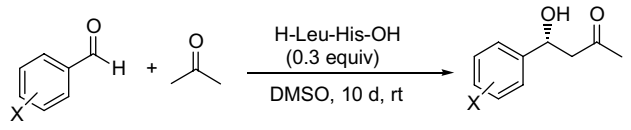
Interestingly, the cyclic dipeptide *cyclo*-[(*S*)-leucyl-(*S*)-histidyl], which has been shown by Inoue et al.[2] to catalyze asymmetric Strecker synthesis, was not active for the direct aldol reaction (Table 1, 24%, 3% ee, entry 7). H-Leu-His-OMe and Z-Leu-His-OMe are less reactive and stereoselective (entries 8 and 9 of Table 1) than H-Leu-His-OH (entry 4), which confirms the importance of the *N*-terminal amino group and, possibly that of the C-terminal carboxyl group (as hydrogen bond donor) for the catalysis.

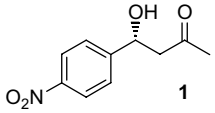
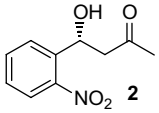
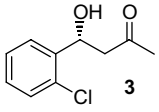
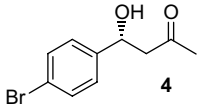
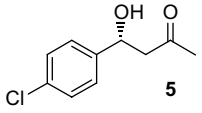
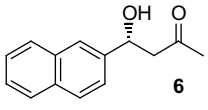
Next, we performed the corresponding reaction with a set of different aromatic aldehydes in the presence of dipeptide H-Leu-His-OH, which appears to be the most effective with respect to the reaction yield (87%) and enantioselectivity (71% ee). We observed that H-Leu-His-OH catalyzed the aldol reaction with varying yields and enantioselectivities, depending on the nature of the substrate used. The formation of different amounts of aldol condensation product was observed as well (Table 2).

Typically, good yields (up to 96%) and enantioselectivities (up to 76% ee) were obtained with electron-deficient aldehydes such as 2- or 4-nitrobenzaldehyde, 2- or 4-chlorobenzaldehyde and 4-bromobenzaldehyde (Table 2, entries 1–5) with respect to less active naphthaldehyde (Table 2, entry 6).

The fact that suitable achiral or chiral additives and co-catalysts can enhance the yield and in many cases also the enantioselectivity as well, which has been discussed in the

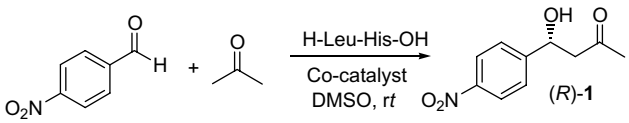
Table 2. Aldol reactions of acetone with several aromatic aldehydes catalyzed by H-Leu-His-OH



Entry	Product	Conv. (%)[a]	Yield (%)[a]	ee (%)[b]
1		96	87	71
2		82	62	72
3		100	96	76
4		89	65	68
5		94	67	60
6		65	53	50

[a] Determined by ^{1}H NMR of crude mixture after completion of the reaction.
[b] Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.

Table 3. Co-catalysts tested for the asymmetric aldol reaction of acetone with 4-nitrobenzaldehyde



Entry	H-Leu-His-OH (equiv)	Co-catalyst (equiv)	Reaction time (h)	Conv. (%)[a]	Yield (%)[a]	ee (%)[b]
1	0.3	(*R*)-2-Methylpiperazine (0.1)	25	80	80	53
2	0.3	(*S*)-2-Methylpiperazine (0.1)	72	90	90	42
3	0.3	L-Norephedrine (0.1)	72	96	86	42
4	0.3	(*R*)-Phenylethylamine (0.1)	72	84	78	43
5	0.3	L-Aspartic acid (0.1)	72	97	87	44
6	0.3	1,1,3,3-Tetramethylguanidine (0.1)	72	91	90	40
7	0.3	*trans*-2,5-Dimethylpiperazine (0.1)	**22**	**97**	**97**[c]	**55**
8	—	(*R*)-2-Methylpiperazine (0.3)	168	56	56	1
9	—	(*S*)-2-Methylpiperazine (0.3)	168	58	48	5
10	—	L-Norephedrine (0.3)	240	72	54	2
11	—	(*R*)-Phenylethylamine (0.3)	240	53	28	4
12	—	L-Aspartic acid (0.3)	120	86	65	14
13	—	1,1,3,3-Tetramethylguanidine (0.3)	4	100	95	—
14	—	*trans*-2,5-Dimethylpiperazine (0.3)	168	28	26	—

[a] Determined by ^{1}H NMR of crude mixture after completion of the reaction.
[b] Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.
[c] Isolated yield after silica gel chromatography.

excellent review by Shibasaki et al.,[24] encouraged further study. The aldol reaction of acetone with 4-nitrobenzaldehyde was examined with H-Leu-His-OH in the presence of different co-catalysts (Table 3).

It is interesting to note that the reaction rate was increased to a different extent, depending on the nature of co-catalyst used. The reaction time was shortened from 10 days (87%, entry 4 of Table 1) to 25 h (80%, entry 1 of Table 3) in the presence of (*R*)-2-methylpiperazine (0.1 equiv), while only to 72 h (90%, entry 2 of Table 3) in the presence of its enantiomer, (*S*)-2-methylpiperazine (0.1 equiv). Similar results (rate enhancement to 72 h) were observed with further chiral co-catalysts: *L*-norephedrine, (*R*)-phenylethylamine and L-aspartic acid (Table 3, entries 3–5).

Interestingly, no condensation product was observed with (*R*)-2-methylpiperazine and (*S*)-2-methylpiperazine (Table 3, entries 1 and 2), while still significant amounts were produced when L-norephedrine, (*R*)-phenylethylamine and L-aspartic acid (Table 3, entries 3–5) were used as co-catalysts.

Next we tested *trans*-2,5-dimethylpiperazine, which has already been described by Hanessian and Pham[25] as an additive for L-proline catalyzed conjugate additions, and 1,1,3,3-tetramethylguanidine as achiral co-catalysts. Whereas the use of *trans*-2,5-dimethylpiperazine alone provides the product in only 26% yield in 168 h (Table 3, entry 14), the 1,1,3,3-tetramethylguanidine alone produces the aldol product with 95% yield in 4 h. Considering these results one might suggest that the application of 1,1,3,3-tetramethylguanidine as co-catalyst could significantly improve the reaction rate with respect to *trans*-2,5-dimethylpiperazine. However, as it was already noted by Shibasaki et al.[24] a priori predictions of which from a variety of additives may be beneficial are hard to make and it is also hard to explain why an additive is beneficial. Indeed, surprisingly, the combination of dipeptide H-Leu-His-OH and 1,1,3,3-tetramethylguanidine gave product with 90% yield and 40% ee in 72 h (Table 3, entry 6), while the H-Leu-His-OH/*trans*-2,5-dimethylpiperazine combination provided aldol with 97% yield and 55% ee in just 22 h (Table 3, entry 7). No condensation product has been observed in both cases. In general, much higher reaction rates in the presence of both dipeptide and co-catalyst with respect to first the dipeptide (Table 1, entry 4) or co-catalysts (Table 3, entries 8–14) indicate the possibility of synergistic effects. The significant increases in the acceleration of the reaction, most remarkable for achiral *trans*-2,5-dimethylpiperazine and the improved yields (up to 97%), were paid for by lower enantioselectivities (up to 55% ee, Table 3, entries 1–7 vs 71% ee, Table 2, entry 1). The results obtained however demonstrate that even with co-catalysts, which give only 0–14% ees, when acting independently (Table 3, entries 8–14), the dominating influence on enantioselectivities comes from the dipeptide H-Leu-His-OH.

These results demonstrate that the use of suitable co-catalysts with matching chirality for this reaction might result in higher yields and enantioselectivities and in markedly accelerated reactions without side products.

3. Conclusion

In summary, we have described here for the first time structure/activity relationships for some linear (*S*)-histidine-based dipeptide catalysts, testing them on known model aldol reactions.

The reactivity and stereoselectivity seems to be dependent upon the intramolecular cooperation of side-chain

functional groups and the presence of a suitable combination and sequence of amino acids.

The synthetic scope of the selected dipeptide catalyst (H-Leu-His-OH) has been demonstrated. Good yields (up to 96%) and enantioselectivities (up to 76% ee) were obtained with electron-deficient aromatic aldehydes.

Furthermore, the influence of different chiral and achiral co-catalysts on the reaction rates, yields and enantioselectivities have been examined. Significant increases in reaction rates, most notable for achiral *trans*-2,5-dimethylpiperazine (22 h of reaction time), and the improved yields (up to 97%) with moderate enantioselectivities (up to 55% ee) were found.

More effective stereochemical features may be observed with other suitable co-catalysts and in different other solvents. This may also be of considerable interest in the study of various co-catalyst's effects, as well as in the detailed mechanistic understanding of the role of co-catalysts and/or additives.

4. Experimental

4.1. General

DMSO was distilled prior to use. Reagents obtained from commercial sources were used without further purification. TLC chromatography was performed on precoated aluminium silica gel SIL G/UV_{254} plates (Marcherey, Nagel Co.) or silica gel 60-F_{254} precoated glass plates (Merck). ^{1}H NMR spectra were recorded with Varian Unity 300.

4.2. General procedure for the aldol reactions

Dipeptide (30 mol %) was added to a dry acetone–DMSO (1:4) mixture and was stirred for 20 min. The aromatic aldehyde (0.05 M) was added and the resulting mixture stirred at room temperature under nitrogen. After completion of the reaction, the mixture worked up as described in the literature.[23] All reaction products had NMR spectra in accordance with the literature data. Enantioselectivities of all products were determined by chiral HPLC analysis (Daicel Chiralpak AS).

4.3. (4*R*)-(4-Nitrophenyl)-4-hydroxy-2-butanone 1

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, 2H), 7.53 (d, 2H), 5.24 (m, 1H), 3.58 (br s, 1H), 2.84 (m, 2H), 2.20 (s, 3H); HPLC: *n*-hexane/2-propanol = 75:25, flow rate 1 ml/min, λ = 254 nm: t_R (major) = 18.84 min, t_R (minor) = 26.58 min.

4.4. (4*R*)-(2-Nitrophenyl)-4-hydroxy-2-butanone 2

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (dd, 1H), 7.88 (dd, 1H), 7.68 (dt, 1H), 7.43 (dt, 1H), 5.60–5.65 (m, 1H), 3.72 (d, 1H), 3.14 (dd, 1H), 2.70 (dd, 1H), 2.21 (s, 3H); HPLC: *n*-hexane/2-propanol = 75:25, flow rate 1 ml/min, λ = 254 nm: t_R (major) = 15.01 min, t_R (minor) = 11.61 min.

4.5. (4*R*)-(2-Chlorophenyl)-4-hydroxy-2-butanone 3

^{1}H NMR (300 MHz, [D_6]DMSO) δ 7.60 (dd, 1H), 7.27–7.42 (m, 3H), 5.53 (d, 1H), 5.38 (m, 1H), 3.33–3.35 (s, 1H), 2.62–2.65 (m, 2H), 2.18 (s, 3H); HPLC: *n*-hexane/2-propanol = 80:20, flow rate 1 ml/min, λ = 210 nm: t_R (major) = 9.38 min, t_R (minor) = 7.68 min.

4.6. (4*R*)-(4-Bromophenyl)-4-hydroxy-2-butanone 4

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, 2H), 7.20 (d, 2H), 5.08–5.12 (m, 1H), 2.80 (m, 2H), 2.19 (s, 3H); HPLC: *n*-hexane/2-propanol = 75:25, flow rate 1 ml/min, λ = 210 nm: t_R (major) = 9.43 min, t_R (minor) = 11.67 min.

4.7. (4*R*)-(4-Chlorophenyl)-4-hydroxy-2-butanone 5

^{1}H NMR (300 MHz, [D_6]DMSO) δ 7.37 (s, 4H), 5.41 (d, 1H), 5.0 (m, 1H), 2.68–2.72 (m, 2H), 2.11 (s, 3H); HPLC: *n*-hexane/2-propanol = 75:25, flow rate 1 ml/min, λ = 210 nm: t_R (major) = 8.82 min, t_R (minor) = 10.86 min.

4.8. (4*R*)-4-(2-Naphthalenyl)-4-hydroxy-2-butanone 6

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80–7.83 (m, 4H), 7.43–7.48 (m, 3H), 5.29–5.34 (m, 1H), 2.91–2.95 (m, 2H), 2.20 (s, 3H); HPLC: *n*-hexane/2-propanol = 90:10, flow rate 1 ml/min, λ = 210 nm: t_R (major) = 21.84 min, t_R (minor) = 23.98 min.

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