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Asymmetric alcoholysis of 2-phenyl-5(4*H*)-oxazolones by the catalytic mixture of cyclo[(*S*)-His-(*S*)-Phe] with chiral auxiliaries

Lunjia Xie,[a] Wenting Hua,[a,*] Albert S. C. Chan [b] and Yun-Chang Leung [b]

[a] *Department of Chemistry, Peking University, Beijing 100871, China*

[b] *Open Laboratory of Chirotechnology and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong, China*

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Abstract

Some derivatives of dipeptides containing a His residue catalyzed the ring opening of 2-phenyl-4-benzyl-5(4*H*)-oxazolone by methanol. The mixture of cyclo[(*S*)-His-(*S*)-Phe] (CHP) with chiral auxiliaries which possess both a hydrogen-bond donor and a hydrogen-bond acceptor was a more effective and enantioselective catalyst than the CHP alone. The influence of racemic and the two enantiomerically pure auxiliaries on the cyclo[(*S*)-His-(*S*)-Phe]-catalyzed alcoholysis of the 5(4*H*)-oxazolone was different. A mixture of CHP with L-diisopropyl tartrate catalyzed the enantioselective ring opening of 2-phenyl-4-benzyl-5(4*H*)-oxazolone by methanol, ethanol and *n*-butanol, preferentially affording the *N*-benzoyl-L-phenylalaninates (20–39% e.e.).

1. Introduction

The importance of optically active natural and unnatural α-amino acids has prompted the development of practical methods for their preparation in an enantiomerically pure form of either configuration. An important and interesting method for the preparation of optically active L-α-amino acids was the lipase-catalyzed dynamic kinetic resolution of racemic 5(4*H*)-oxazolones by alcohols.[1] However, in general, the inherent disadvantages of enzymatic methods such as the specificity and instability of enzymes are difficult to overcome. Narrow substrate tolerance and selection of L-configured enantiomers limit the scope of the enzymatic method.

Nonenzymatic catalysts are often used for a wider scope of substrates. Moreover, desired configuration and high enantioselectivity of the product may be achieved by the proper design of the nonenzymatic catalysts. Nonenzymatic catalytic enantioselective hydrolysis[2] and stoichiometric enantioselective

* Corresponding author.

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alcoholysis[3] of racemic 5(4*H*)-oxazolones have been reported. Because 5(4*H*)-oxazolones are easily hydrolyzed without catalysts, we have sought to devise a method for the catalytic enantioselective alcoholysis of racemic 5(4*H*)-oxazolones. We found that cinchona alkaloids could be used as nonenzymatic catalysts for enantioselective methanolysis of 2-phenyl-5(4*H*)-oxazolones,[4] but derivatives of the hydroxyl at C_9 of cinchona alkaloids showed almost no catalytic activity.[5] Fu et al. also investigated enantioselective methanolysis of 2-phenyl-5(4*H*)-oxazolones catalyzed by a planar-chiral derivative of 4-(dimethylamino)pyridine.[6]

Since lipases catalyze ring opening of 5(4*H*)-oxazolones by alcohols[1] and lipases contain essential histidine residues in their active sites,[7] we used derivatives of dipeptides containing a histidine residue as nonenzymatic catalysts for the enantioselective alcoholysis of 2-phenyl-4-benzyl-5(4*H*)-oxazolone. Indeed, dipeptides and cyclo dipeptides, which contain a histidine residue, have been used for hydrolysis of *p*-nitrophenyl carboxylate[8] and for the asymmetric hydrocyanation of benzaldehyde.[9] More rigid cyclo dipeptides gave higher enantiomeric excesses of cyanohydrins than linear dipeptides.[9a] Of the cyclo dipeptides, cyclo[(*S*)-His-(*S*)-Phe] (CHP) or cyclo[(*R*)-His-(*R*)-Phe] is the most enantioselective catalyst reported by Inoue et al. and others.[9] Although CHP and its enantiomer has proved to be effective in the production of optically active cyanohydrins from aromatic aldehydes and HCN, to date no satisfactory explanations for the enantioselectivity and autocatalysis exist.[10] The structure of active CHP and the structure of the complexes of CHP with cyanohydrins are unclear.[10b] We have proposed a new mechanistic model for the asymmetric addition of HCN to aldehydes catalyzed by CHP based on known results. We have presented the possible structure of active CHP as a catalyst and presumed the structure of the complex of CHP with a cyanohydrin as a more effective and enantioselective catalyst to explain autocatalysis and enantioselective autoinduction.[11]

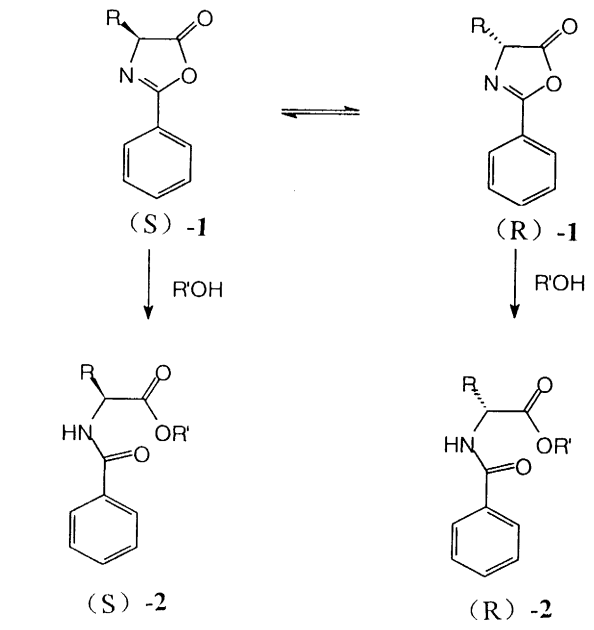
Here, we report the use of linear dipeptides and cyclo dipeptides containing histidine residues as catalysts for the alcoholysis of 2-phenyl-4-benzyl-5(4*H*)-oxazolone, and present an application of the mechanistic model for the asymmetric hydrocyanation of aldehyde[11] to catalytic alcoholysis of the 5(4*H*)-oxazolone by the mixture of CHP with chiral auxiliaries. We also try to explain why the proposed complexes of CHP with auxiliaries are more effective and enantioselective catalysts than CHP.

2. Results and discussion

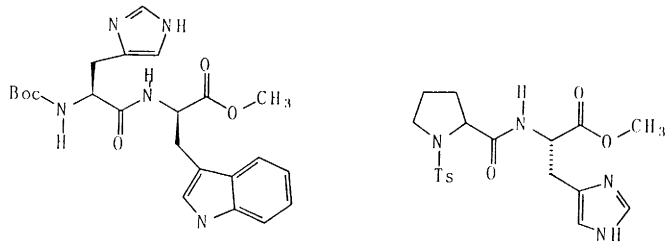
2.1. Derivatives of dipeptides as catalysts

(±)-2-Phenyl-4-benzyl-5(4*H*)-oxazolone [(±)-**1**] was selected as the substrate for our initial studies, since the configuration of product **2** could be deduced by comparing the specific rotation of **2** to that of authentic **2** (*R* or *S*) and the e.e. of **2** and its configuration could be determined by capillary electrophoresis.[12] Derivatives of dipeptides (**3**–**8**) catalyzed the ring opening of (±)-**1** using methanol as the nucleophile in organic solvents. The reactions carried out in the appropriate solvent [100 mL/substrate (g)] by using the following mol ratio: substrate:methanol:catalyst=1:6.2:0.5–0.6. The percentage conversion of **1** into **2** was determined from the ^{1}H NMR spectra of the products or deduced from the TLC by comparing the reaction mixture with the mixture of known mol ratios of **1** and **2** at the same molar concentration. The derivatives of dipeptides which were soluble in organic solvents (**4**–**6**) were more effective catalysts than insoluble derivatives of dipeptides (**3**, **7** and **8**) (see Scheme 1 and Table 1).

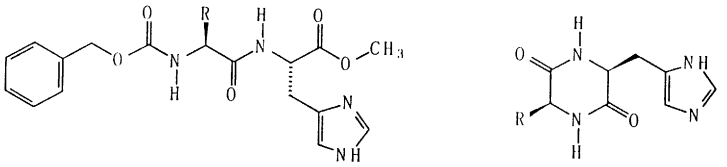
Since cyclo[(*S*)-His-(*S*)-Phe] (CHP) or its enantiomer were the most effective and enantioselective catalysts of the derivatives of dipeptides for the asymmetric hydrocyanation of aldehydes, this suggested that CHP **8** might be the most effective and enantioselective catalyst for ring opening of (±)-**1**. However,



R=PhCH$_2$



3 **4**



5 (R=Me)

6 (R=PhCH$_2$)

7 (R =Me)

8 (R=PhCH$_2$)

Scheme 1.

Table 1
Methanolysis of (±)-**1** by derivatives of dipeptides

No	Cat	Cat/Sub	solvent	T(℃)	Time(h)	Conv.	% e.e.	Conf.
1	**3**	0.55	$CHCl_3$	11	4.5	<10%	/	/
2	**3**	0.55	$CHCl_3$	25	71	~50%	/	/
3	**4**	0.5	$CH_3C_6H_5$	12	17	>80%	/	/
4	**4**	0.5	$CH_3C_6H_5$	12	28	>90%	6	S
5	**5**	0.5	$CHCl_3$	29	1	~50%	/	/
6	**5**	0.5	$CHCl_3$	29	6	>90%	5	S
7	**6**	0.5	$CHCl_3$	20	16.5	>80%	6	S
8	**7**	0.6	$CHCl_3$	31	16	~25%	/	/
9	**7**	0.6	$CHCl_3$	31	42	~50%	<1	S
10	**8**	0.5	$CHCl_3$	25	41.5	~50%	/	/
11	**8**	0.5	$CHCl_3$	25	67.5	75%	<1	R
12	**8**	0.5	$CH_3C_6H_5$	13-14	94.5	<10%	/	/
13	**8**	0.5	$CH_3C_6H_5$	25	90	75%	<1	R
14	**8**	0.5	CH_2Cl_2	13.5	118	<10%	/	/
15	**8**	0.5	CH_2Cl_2	25	66	~30%	/	/
16	**8**	0.5	CH_2Cl_2	25	90	43%	4	R
17	/	/	$CHCl_3$	25	41.5	~0%	/	/
18	/	/	$CH_3C_6H_5$	14-16	63	~0%	/	/
19	/	/	CH_2Cl_2	13.5	118	~0%	/	/
20	/	/	CH_2Cl_2	25	63	~0%	/	/

results showed that CHP (**8**) was less effective and enantioselective than linear dipeptides (**4**, **5** and **6**). We, therefore, studied the mechanistic model for the asymmetric addition of HCN to aldehydes catalyzed by CHP based on known results. We also analyzed the reasons why CHP was not an effective and enantioselective catalyst for ring opening of (±)-**1** by methanol. In addition, we devised the mixture of CHP with chiral auxiliaries as catalysts for the alcoholysis of (±)-**1**.

2.2. Mixture of CHP with chiral auxiliaries as catalysts

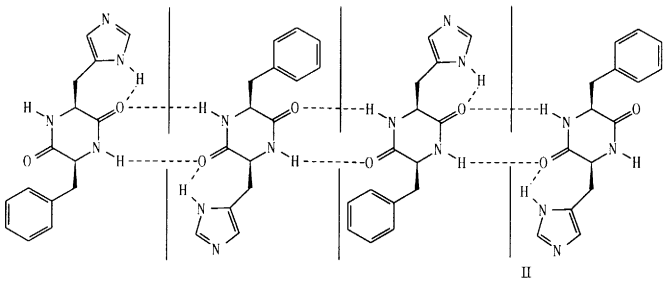
From the studies of the mechanistic models for the asymmetric addition of HCN to aldehydes catalyzed by CHP, we postulated[11] that part of the structure of active CHP in solid state was **A** and the structure of the complex of CHP with a cyanohydrin was **B**, and a new mechanistic model for asymmetric addition of HCN to benzaldehyde is shown in Fig. 1. By an application of these ideas to the catalytic alcoholysis of (±)-**1** by CHP, methanolysis of (±)-**1** is catalyzed by an active part of the hydrogen-bonded polymer of CHP (Fig. 2). Unlike a cyanohydrin which broke the hydrogen bonds of the CHP polymer[13] and formed the catalytic complex with CHP, the product of methanolysis of (±)-**1**, *N*-benzoyl phenylalanine methyl ester (**2**, R′=Me), could not break the hydrogen bonds of the CHP polymer, for **2** might exist as either a *trans* **C** or *cis*-dimer **D** or **E** instead (Fig. 3) of forming a complex with CHP. We supposed that the catalytic activity of CHP could be liberated by breaking the hydrogen bond of the CHP polymer and the enantioselectivity of CHP could be enhanced by forming complexes between CHP and chiral auxiliaries which possessed both a hydrogen-bond donor and a hydrogen-bond acceptor like cyanohydrins. Therefore, various auxiliaries of (±)-**1**, including A1 (L-diisopropyl tartrate), A2 (D-diisopropyl tartrate), A3 (L-diethyl tartrate), A4 [(±)-ethyl lactate], A5 [(*S*)-ethyl lactate], A6 [(R)-methyl lactate], A7 [(±)-lactic acid], A8 (L-tartaric acid), A9 (L-proline), A10 [(±)-proline], A11 (L-menthol), A12 [(±)-menthol], A13 (benzyloxycarbonyl-L-leucyl-glycine ethyl ester), A14 (L-arginine·HCl), A15 (L-leucine), A16 [(±)-leucine], A17 (phthalimide), A18 (benzoic acid) and A19 [(4*S*)-2-(2-hydroxyl phenyl)-4-(2-methylpropyl)oxazoline]. The structure **F** (Fig. 4) represents the possible complex of CHP with a chiral auxiliary (α-hydroxyl carboxylic ester).

The results of preliminary investigations on the methanolysis of (±)-**1** catalyzed by the mixture of CHP and an auxiliary are summarized in Table 2 (CHP:auxiliary=1:4) and Table 3 (CHP:auxiliary=1:1). Among the 19 auxiliaries examined, L-diisopropyl tartrate (A1) was best suited for further investigation (see Tables 4 and 5). From Tables 2–5, the mol ratio of substrate, methanol and CHP was 1, 6.2 and 0.5.

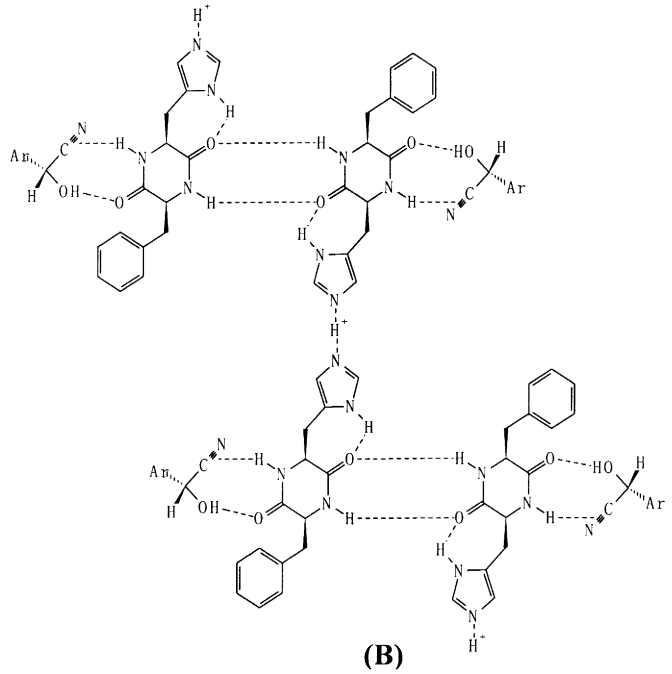
The results in Tables 2 and 3 support our arguments: the catalytic activity of CHP could be liberated by breaking the hydrogen bonds of the CHP polymer and the enantioselectivity of CHP could be enhanced by forming the proposed complexes between CHP and chiral auxiliaries which possess both a hydrogen-bond donor and a hydrogen-bond acceptor.

The percentage conversion of **1** into **2** was about 50% at 15–16°C for 2 days with the mixture of CHP and L-diisopropyl tartrate (A1), while the percentage conversion was less than 10% at 13–14°C for 4 days with only CHP. The conversion of the reaction catalyzed by the mixture of CHP and A1 was almost complete at 15–16°C for 6 days and the enantiomeric excess of the product **2** was 27%, whereas the conversion of the reaction catalyzed by only CHP was 75% at 25°C for 4 days with almost no enantioselectivity (see entries 21, 22, 35 and 36).

The influence of two enantiomeric auxiliaries on CHP-catalyzed methanolysis of (±)-**1** was different. The enantioselectivity of the reaction catalyzed by the mixture of CHP and L-diisopropyl tartrate was 27% e.e., whereas that of the reaction catalyzed by the mixture of CHP and D-diisopropyl tartrate was only 2% e.e. (see entries 21 and 23). Because the configuration of C_2 and C_3 of L-diisopropyl tartrate is *R*, the hydroxyl group at C_2 and the carbonyl group at C_1 of L-diisopropyl tartrate may form hydrogen bonds with the carbonyl group at the phenylalanine residue and the amido NH group at the histidine residue of cyclo[(*S*)]His-(*S*)-Phe] (CHP), respectively, for the steric hindrance of the phenyl group at CHP with the R group at L-diisopropyl tartrate (see structure **F** (Fig. 4)). On the contrary, the configuration of C_2 and C_3 of D-diisopropyl tartrate is *S*. The D-diisopropyl tartrate may not form two similar hydrogen bonds with CHP because of steric hindrance. This explains why L-diisopropyl tartrate was a better auxiliary than D-diisopropyl tartrate on enantioselectivity and rate of reaction.



(A)



(B)

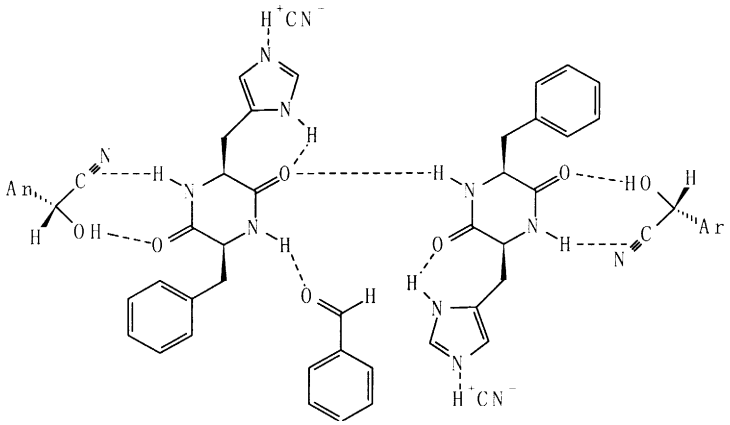


Fig. 1.

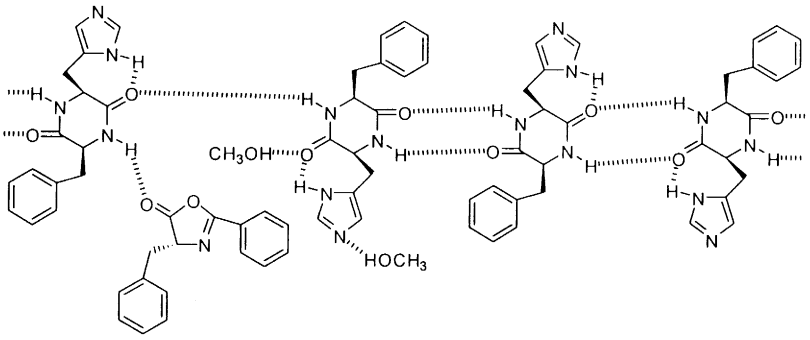
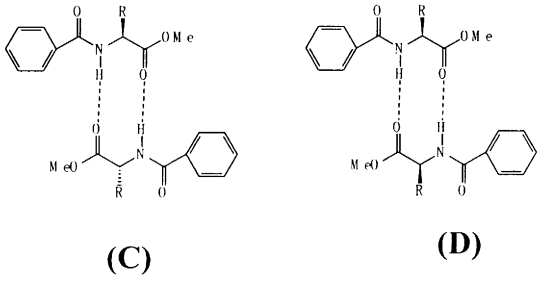
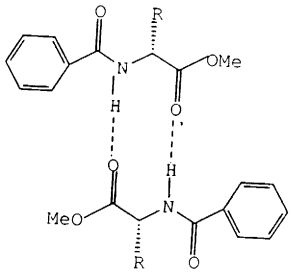


Fig. 2.



(C) **(D)**

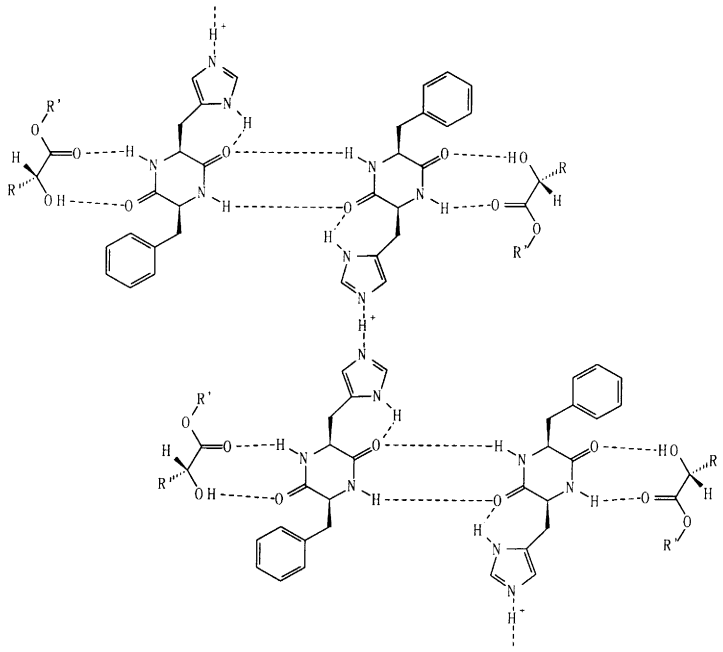


(E)

Fig. 3.

For the same reason, it is difficult for (*S*)-ethyl lactate to form the two hydrogen bonds with CHP. Therefore, the percentage conversion was less than 10% at 15–16°C for 8 days with (*S*)-ethyl lactate (A5) as an auxiliary. But the percentage conversion was more than 50% with (±)-ethyl lactate (A4) because (±)-ethyl lactate contained (*R*)-ethyl lactate which could form the two hydrogen bonds with CHP (see entries 25 and 26). (*R*)-Methyl lactate (A6) or (±)-lactic acid (A7) were also better auxiliaries than A5 (see entries 27 and 28).

L-Amino acids with aliphatic side chains such as L-proline (A9) and L-leucine (A15) may form two hydrogen bonds with CHP in either the **G** or **H** structure (complex of CHP with A15). *R* and *S* isomers of racemic amino acids with aliphatic chains might form cyclic dimers (**I**) by two hydrogen bonds (Fig. 5).



(F)

Fig. 4.

The L-amino acids were better auxiliaries than their racemates for methanolysis of (±)-**1** catalyzed by CHP with auxiliaries because the L-amino acids might form complexes with CHP (see entries 30, 31 and 40–43).

A13 and A19 might also form complexes with CHP (see structures **J** and **K** (Fig. 6)). The complexes were better catalysts than CHP (see entries 35, 36, 38 and 47). A18 or A19 could not catalyze methanolysis of (±)-**1**, but the mixture of CHP with A18, A19 or both could catalyze the reaction and were more effective and enantioselective than CHP. The auxiliaries, which could not form stable cyclic complexes with CHP (A11, A12 and A17), had little influence on catalytic activity of CHP. Unlike A18 or A19, A1 was also a catalyst. The results of methanolysis of (±)-**1** by A1 and/or other catalysts are shown in Table 4.

In order to improve enantioselectivity, we used less acidic and more steric alcohols (ethanol or *n*-BuOH) as the nucleophile for the ring opening of (±)-**1** utilizing the mixture of CHP and A1 as the catalyst. The percent enantiomeric excess of **2** (R′=Et) was 39% e.e. for ethanol and that of **2** (R′=*n*-Bu) was 35% e.e. for *n*-BuOH.

The imidazole group on the CHP and in other dipeptides containing His residue acts as either base or nucleophilic catalyst for the ring opening of 2-phenyl-4-benzyl-5(4*H*)-oxazolone **1**, because imidazole can take part in either base or nucleophilic catalysis for an ester hydrolysis or acyl transfer depending on the structure of the ester[7] and **1** is an activated ester. The role of the imidazole group in either base or nucleophilic catalysis also depends on the structure of a nucleophilic agent. The imidazole group may act as a more effective base catalyst in the methanolysis of **1**, although the imidazole group can still take part in nucleophilic catalysis in the reaction. The nucleophilic catalysis becomes relatively more effective

Table 2
Methanolysis of (±)-**1** by mixture of CHP and auxiliaries (CHP/aux.=1/4)

No	Auxiliary	Conf.	solvent	T(℃)	Time(d)	Conv.	% e.e.	Conf.
21	A1	L	$CH_3C_6H_5$	15~16	6	>99%	27	S
22	A1	L	$CH_3C_6H_5$	15~16	2	~50%	/	/
23	A2	D	$CH_3C_6H_5$	15~16	6	>80%	2	S
24	A3	L	$CH_3C_6H_5$	12	6	>99%	1	R
25	A4	dl	$CH_3C_6H_5$	15~16	8	>50%	0	/
26	A5	S	$CH_3C_6H_5$	15~16	8	<10%	/	/
27	A6	R	$CH_3C_6H_5$	12	6	>50%	2	R
28	A7	dl	$CH_3C_6H_5$	12	5	>99%	<1	R
29	A8	L	$CH_3C_6H_5$	15~16	8	<10%	/	/
30	A9	L	$CH_3C_6H_5$	15~16	5	>99%	9	S
31	A10	dl	$CH_3C_6H_5$	15~16	6	>80%	1	R
32	A11	dl	$CH_3C_6H_5$	15~16	2	<10%	/	/
33	A12	L	$CH_3C_6H_5$	13.5~15	2	<10%	/	/
34	A12	L	$CH_3C_6H_5$	13.5~15	8	~30%	/	/
35	/	/	$CH_3C_6H_5$	13~14	4	<10%	/	/
36	/	/	$CH_3C_6H_5$	25	4	75	<1	R

as the base catalysis is inhibited by using less acidic and more steric alcohols as nucleophiles. So, the enantioselectivity of the catalysis increases (see Table 5). The enantioselectivity of products depends on the relative effectiveness of nucleophilic or base catalysis.

3. Conclusion

Derivatives of dipeptides containing a His residue can be used to catalyze the alcoholysis of 2-phenyl-4-benzyl-5(4*H*)-oxazolone. The rate of reaction depends on the solubility of the dipeptides. Mixtures of cyclo[(*S*)-His-(*S*)-Phe] (CHP) with auxiliaries are more effective and enantioselective catalysts than the CHP alone.

4. Experimental

4.1. General

Melting points are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter with a 1 dm cell. ^{1}H NMR spectra were recorded on a Bruker AKX-400 (400 MHz) spectrometer. IR spectra were recorded on a Bruker Vector Series spectrometer.

Table 3
Methanolysis of (±)-**1** by a mixture of CHP and auxiliaries (CHP/aux.=1)

No	Auxiliary	Conf.	solvent	T(℃)	Time(d)	Conv.	% e.e.	Conf.
37	A13	L	$CHCl_3$	12	9	<10%	/	/
38	A13	L	$CH_3C_6H_5$	12-14	9	>80%	5%	R
39	A14	L	$CH_3C_6H_5$	14	3	~75%	/	/
40	A15	L	$CH_3C_6H_5$	14-16	3	~75%	/	/
41	A15	L	$CH_3C_6H_5$	14-16	9	>80%	5	R
42	A16	dl	$CH_3C_6H_5$	14-16	3	~30%	/	/
43	A16	dl	$CH_3C_6H_5$	14-16	9	>50%	6	R
44	A17	/	$CH_3C_6H_5$	14-16	2	~10%	/	/
45	A17	/	$CH_3C_6H_5$	14-16	9	<30%	/	/
46	A18	/	$CH_3C_6H_5$	15	2	>90%	4	R
47	A19	S	$CH_3C_6H_5$	14-16	3	~75%	6	R
48	A18+A19	S	$CH_3C_6H_5$	14	1	~75%	/	/
49	A18+A19	S	$CH_3C_6H_5$	14	2	>90%	4	R

Table 4
Methanolysis of (±)-**1** by a catalyst and/or A1

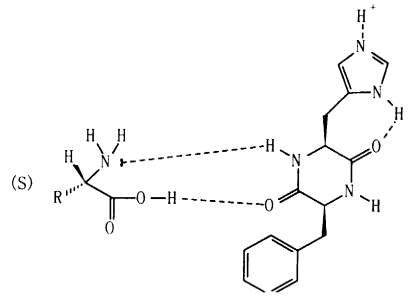
No	Cat.	Aux.	Aux./Sub	Solvent	T(℃)	Time(d)	Conv.	% e.e.	Conf.
21	CHP	A1	2	$CH_3C_6H_5$	15-16	6	>99%	27	S
50	CHP	A1	2	$CH_3C_6H_5$	14	10	>75%	20	S
36	CHP	/	/	$CH_3C_6H_5$	25	4	75%	<1	R
51	/	A1	2	$CH_3C_6H_5$	14	10	>80%	6	R
52	CHP,Et_3N^a	A1	2	$CH_3C_6H_5$	14	10	>75%	3	S
53	Et_3N^a	A1	2	$CH_3C_6H_5$	14	10	~50%	6	R
54	Et_3N^b	/	/	$CH_3C_6H_5$	14	8	~50%	/	/
55	CHP	A1	2	$CHCl_3$	14	8	>80	1	R

(a): Et_3/Sub. =0.2 (mol/mol)
(b): Et_3/Sub. =0.5 (mol/mol)

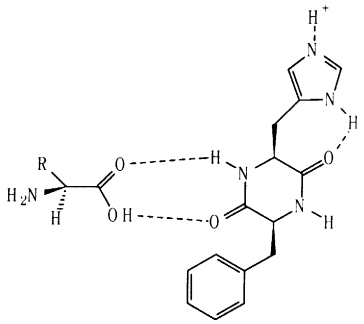
For the determination of e.e., the *N*-benzoyl-phenylalanine esters were first hydrolyzed into *N*-benzoyl-phenylalanine by NaOH and then analyzed by aqueous capillary electrophoresis using β-CD as chiral selector.[12]

Table 5
Alcoholysis of (±)-**1** by the complex of CHP and A1 in toluene

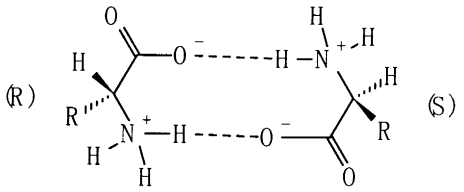
No	Aux.	Aux./CHP	ROH	ROH/Sub	T(℃)	Time(d)	Conv.	% e.e.	conf.
56	A1	1	EtOH	4	12-14	15	>30%	39	S
57	A1	1	BuOH	2	12-14	15	>40%	35	S
58	A1	1	MeOH	6.2	12-14	15	>40%	2	R
50	A1	4	MeOH	6.2	14	10	>75%	20	S



(G)

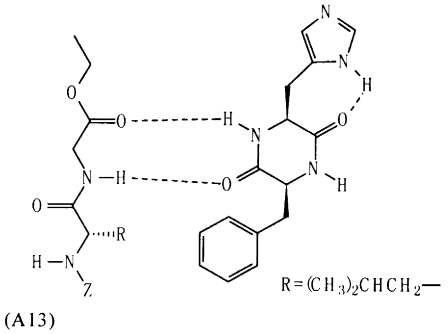


(H)



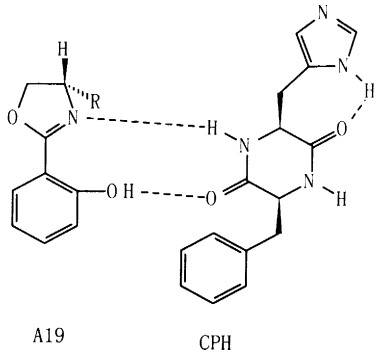
(I)

Fig. 5.



(A13)

(J)



A19 CPH

(K)

Fig. 6.

4.2. (±)-2-Phenyl-4-benzyl-5(4H)-oxazolone **1**

Compound **1** was prepared from *N*-benzoyl-phenylalanine according to literature procedure.[2a] Yield 80%; mp: 66–68°C (lit.:[2a] mp: 70–71°C). IR (cm^{-1}): 1812, 1754. ^1H NMR (ppm, $CDCl_3$): δ 3.20 (dd, 1H, J=6.4, 14 Hz), 3.40 (dd, 1H, J=5.2, 14 Hz), 4.71 (dd, 1H, J=5.2, 6.4 Hz), 7.22–7.29 (m, 5H), 7.44 (m, 2H), 7.55 (m, 1H), 7.94 (m, 2H).

4.3. N-Tosyl-(S)-prolyl-(S)-histidine methyl ester **4**

(*S*)-Histidine methyl ester dihydrochloride (100 mg) was suspended in $CHCl_3$ (1.5 mL) and Et_3N (0.125 mL) was added. The mixture was stirred and cooled in an ice–salt bath (−5°C). A solution of *N*-tosyl-(*S*)-prolyl chloride[14] (120 mg) in $CHCl_3$ (5 mL) was added dropwise and Et_3N (0.06 mL) was added again. The mixture was stirred overnight. $CHCl_3$ (5 mL) was added and the reaction mixture was extracted with water then with aqueous ammonia (0.05 mol dm^{-3}) and finally with water. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuum to give 170 mg of **4** as an oily solid. Crystallization from benzene–petroleum ether (30–60°C) gave 110 mg (yield 63.4%) of white solid; mp: 57.5–59.5°C. IR (cm^{-l}): 3399, 2955, 1745, 1672, 1347, 1160, and 1092. ^1H NMR (ppm, $CDCl_3$): δ 1.6 (m, 1H), 1.70 (m, 1H), 1.86 (m, 1H), 2.03 (m, 1H), 2.44 (s, 3H), 3.13–3.27 (m, 3H), 3.62 (m, 1H), 3.75 (s, 3H), 4.31 (dd, 1H, J=3.1, 8.7 Hz), 4.80 (m, 1H), 6.98 (s, 1H), 7.36 (s, 1H), 7.37 (d, 2H, J=8.1 Hz), 7.69 (s, 1H), 7.86 (d, 2H, J=8.2 Hz), 8.54 (d, 1H, J=8 Hz). FABMS 421 $[M+H]^+$.

4.4. Benzyloxycarbonyl-(S)-alanyl-(S)-histidine methyl ester **5**

Compound **5** was prepared from benzyloxycarbonyl-(*S*)-alanine-*p*-nitrophenyl ester and (*S*)-histidine methyl ester dihydrochloride according to the literature.[15] Yield 53%; mp: 164–166 (lit.:[9c] mp: 168–169). IR (cm^{-1}): 3379, 3248, 2990, 2852, 1732, 1702, 1649, 1566, 1505, 1456, 1379, 1340, 1291, 1235. ^1H NMR (ppm, $CDCl_3$): δ 1.41 (d, 3H, J=7.2 Hz), 3.19 (m, 2H), 3.74 (s, 3H), 4.25 (dq, 1H, J=6.8, 7 Hz), 4.80 (m, 1H), 5.09 (d, 1H, J=12.4 Hz), 5.13 (d, 1H, J=12.2 Hz), 5.53 (d, 1H, J=6.4 Hz), 6.82 (s, 1H), 7.33 (m, 6H), 7.7 (s, 1H).

4.5. Benzyloxycarbonyl-(S)-phenylalanyl-(S)-histidine methyl ester **6**

Compound **6** was prepared from benzyloxycarbonyl-(*S*)-phenylalanine-*p*-nitrophenyl ester and (*S*)-histidine methyl ester dihydrochloride according to the literature.[15] Yield 76%; mp: 128–138°C (lit.:[15] yield 39%; mp: 146–154°C; lit.:[9c] yield 77%; mp: 114–116°C). IR (cm^{-1}): 3312, 3013, 2952, 2854, 1743, 1699, 1648, 1532, 1440, 1391, 1256, 1215. ^1H NMR (ppm, $CDCl_3$): δ 2.95–3.15 (m, 4H), 3.68 (s, 3H), 4.39 (m, 1H), 4.75 (m, 1H), 5.07 (s, 2H), 5.43 (d, 1H, J=7.2 Hz), 6.72 (s, 1H), 7.18 (m, 11H, ArH and CONH), 7.47 (s, 1H), 8.1 (bs, 1H).

4.6. (3S,6S)-3-(4-Imidazolylmethyl)-6-methylpiperazine-2,5-dione **7**

Compound **7** was prepared from **5** according to the literature.[15] Yield 79%; mp: 224–235°C (lit.:[9c] mp: 245–250°C). IR (cm^{-1}): 3320, 3127, 2982, 2840, 1664, 1423, and 1312. ^1H NMR (ppm, $(CD_3)_2SO$): δ 1.16 (d, 3H, J=7.2 Hz), 3.08 (m, 2H), 3.90 (q, 1H, J=6.9 Hz), 4.24 (t, 1H, J=5.42 Hz), 7.34 (s, 1H), 8.12 (s, 1H), 8.27 (s, 1H), 8.93 (s, 1H), 14.16 (bs, 2H).

4.7. (3S,6S)-3-Benzyl-6-(4-imidazolylmethyl)piperazine-2,5-dione **8**

Compound **8** was prepared from **6** according to the literature.[9b] Yield 76%; mp: 249–252 (dec.) (lit.:[9b] 248–251°C), $[\alpha]_D^{30}$ −65.8 (c=0.52, AcOH) [lit.:[9b] $[\alpha]_D^{25}$ −65.2 (c=1.97, AcOH)]. IR (cm^{-1}): 3424, 3195, 1673, 1458, and 1339. ^1H NMR (ppm, $(CD_3)_2SO$): δ 1.57 (dd, 1H, J=9.1, 14.5 Hz), 2.55 (dd, 1H, J=3.6, 14.5 Hz), 2.81 (dd, 1H, J=4.9, 13.5 Hz), 2.87 (dd, 1H, J=4.7, 13.5 Hz), 3.84 (d, 1H, J=8.9 Hz), 4.14 (s, 1H), 6.61 (s, 1H), 7.15 (d, 2H, J=6.9 Hz), 7.23 (m, 1H), 7.3 (t, 2H, J=7 Hz), 7.57 (s, 1H), 7.79 (s, 1H), 8.11 (s, 1H), 11.90 (bs, 1H, NH). FABMS 285 $[M+H]^+$.

4.8. Benzyloxycarbonyl-L-leucyl-glycine ethyl ester A13

Et_3N (0.49 mL) was added to a suspension of glycine ethyl ester hydrochloride (0.5 g) in $CHCl_3$ (10 mL), and stirred at 14°C for 10 min. Benzyloxycarbonyl-(*S*)-leucyl-*p*-nitrophenyl ester (1.38 g), dissolved in $CHCl_3$ (9 mL), was added dropwise and Et_3N (0.5 mL) was added again. The mixture was stirred at 14°C for 11 h, and imidazole (0.050 g) was added. Then the mixture was stirred for 23 h, and $CHCl_3$ (5mL) was added. The solution was extracted with water, aqueous ammonia, water, diluted hydrochloric acid and water. The organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuum to gave 1.31 g (yield ~100%) of colorless crystals, mp: 100–101°C. IR (cm^{-1}, Nicolet MX-S spectrometer): 3300, 3080, 2960, 2920, 2880, 1720, 1680, 1620, 1540, 1500, 1470, 1360, 1300, 1230, 1040. ^1H NMR (ppm, $CDCl_3$): δ 0.94 (d, 6H, J=6 Hz), 1.27 (t, 3H, J=7.2 Hz), 1.54 (m, 1H), 1.67 (m, 2H), 3.98 (s, 2H), 4.20 (q, 2H, J=7.2 Hz), 4.26 (s, 1H), 5.09 (d, 1H, J=12.2 Hz), 5.12 (d, 1H, J=12.2 Hz), 5.30 (d, 1H, J=8.1 Hz), 6.66 (s, 1H), 7.26–7.37 (m, 5H).

4.9. Methanolysis of (±)-**1** by dipeptide derivatives

To the solution of (±)-**1** (10 mg) in $CHCl_3$ (1 mL) was added benzyloxycarbonyl-(*S*)-phenylalanyl-(*S*)-histidine methyl ester (10 mg). The mixture was stirred at 20°C. The progress of the reaction was monitored by TLC using the solvent system ethyl acetate:hexane (2:3). The products were separated and purified by preparative TLC; 6% e.e. of (*S*)-**2** was obtained.

4.10. Enantioselective methanolysis of (±)-**1** by CHP with auxiliaries

To a suspension of CHP (6 mg) in toluene (1 mL) was added L-(±)-diisopropyl tartrate (ca. 0.017 mL). The mixture was stirred at room temperature (15.5°C) for 1 h and 40 min. Then to the mixture were added (±)-**1** (10 mg) and MeOH (0.01 mL). The reaction mixture was stirred for 6 days. The product, purified by preparative TLC, gave 27% e.e. of (*S*)-**2**.

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