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Asymmetric Reformatsky Reaction Induced by Dipeptides

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Abstract: For the first time, synthetic dipeptides were applied to the catalysis of asymmetric Reformatsky reaction. Review in this domain & factors influencing enantioselectivity were discussed.

Keywords: Dipeptide derivative, chiral ligands, catalysis, asymmetric Reformatsky reaction,.

The Reformatsky reaction is an important organic reaction used to synthesize β-hydroxyesters. Some recent developments of this reaction were reviewed in several papers[1].

Efforts to get the asymmetric catalysts of Reformatsky reaction can be dated back to 1973, initiated by M.Guettè, *etc*.[2], with the catalyst of sparteine. In 1991, amino alcohol, another kind of catalyst, was used for this reaction[3]. To increase the enantioselectivity, various amino alcohols were investigated shortly after that[4]. Despite of a few satisfactory cases, the present advance in this domain is not ideal enough as a whole, since the e.e.% values of the majority are lower than 70% and the chemical yields are rather poor. Several improving attempts were reported recently, including the activation of Zn with the employment of Zn-Cu couple[5,6,7] or trimethylchlorosilane[8], the application of metal ions other than Zn(II)[9] and the tailoring of the structures of the substrate esters[1,10].

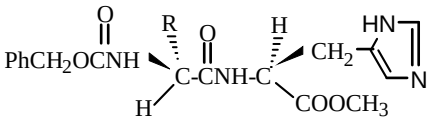
However, new type catalysts were rarely involved. Here, we focus our intention on synthetic dipeptides, a new class of catalysts.

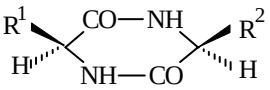
Synthetic peptides are of much interest since 1976, due to their presumable stereoselectivity in asymmetric catalysis, similar to the natural enzymes. In this paper, three categories of dipeptides, listed below, were firstly employed to the inducement of Reformatsky reaction of benzaldehyde and different alkyl bromoacetates.

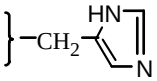
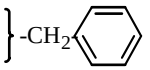
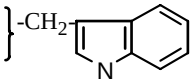
Results and Discussion

The results in **Table 1,2** and **3** are all from the practice of the scheme below. They are designed to gain the understanding of some factors effecting the enantioselectivity.

Category 1, Derivative of linear dipeptides

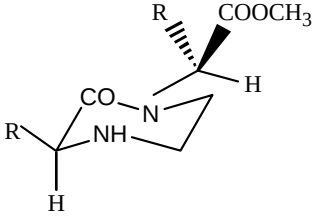


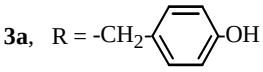


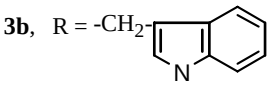
Catalyst	R^1	R^2
2a,	CH_2Ph	
2b,	CH_3	
2c,	CH_2Ph	
2d,	$(CH_2)_2SCH_3$	
2e,	CH_3	
2f,	CH_2Ph	

Category 2, Cyclodipeptides

1a, R = CH_3
1b, R = CH_2Ph
1c, R = $(CH_2)_2SCH_3$



3a, R = 

3b, R = 

Category 3, Pseudo-cyclodipeptides

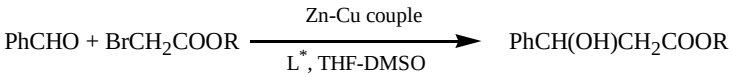


Table 1[a], Factors influencing enatioselectivity(1) — different chiral ligands.

Entry	L*	Molar ratio L*/PhCHO	Reaction Time(h)	Chemical Yield(%)	e.e%[b]	Config.[b]
1	**2a**	0.4	42	71	7.01	S
2	**2b**	0.1	48	31	12.75	S
3	**2c**	0.05	44	81	3.5	S
4	**2d**	0.3	48	54	22.5	R
5	**2e**	0.4	48	89	13.55	S
6	**2f**	0.1	42	65	7.86	S
7	**1a**	0.5	52	74	3.37	S
8	**1b**	0.25	52	71	6.19	S
9	**1c**	0.2	48	78	1.34	S
10	**3a**	0.5	48	46	16.23	S
11	**3b**	0.5	58	58	6.37	R

a. The substrate ester involved here is :$BrCH_2COOC_2H_5$.
b. Determined by polarimetry and the reported value of S-(-)-ethyl β-hydroxyl β-phenyl propionate: $[\alpha]_D^{22}$=-54.9 (c3.5, $CHCl_3$)[8,11,12].

Table 2, Factors influencing enantioselectivity(2) — different ratio of catalyst to substrate [a].

Entry	Molar ratio, L*/PhCHO	Chemical Yield(%)	e.e%[b]	Config. [b]
1	0.025	82	1.8	S
2	0.05	87	2.55	S
3	0.1	74	4.19	S
4	0.4	71	7.01	S

a. The common substrate ester and catalyst involved here: $BrCH_2COOC_2H_5$ & **2a**.
b. Determined by polarimetry and the reported value of S-(-)-ethyl β-hydroxyl β-phenyl propionate: $[\alpha]_D^{22}$=-54.9 (c3.5, $CHCl_3$)[8,11,12].

Table 3, Factors influencing enatioselectivity(3) — different substrate esters.

Entry	L*	Molar ratio L*/PhCHO	Alkyl group R of esters	Chemical Yield(%)	e.e.%	Config.
1	**2a**	0.4	Et	89	13.55	S
2	**2d**	0.3	Et	54	22.5	R
3	**2e**	0.4	t-Bu	66	30.56[a]	S
4	**2d**	0.5	t-Bu	53	35.89[a]	R
5	**2e**	0.5	(-)-Menthyl	72	61.2[b]	S
6	**None**	--	(-)-Menthyl	79	1.6[b]	S

a. Determined by polarimetry and the reported value of S-(-)-t-butyl β-hydroxyl β-phenyl propionate: $[\alpha]_D^{25}$=-32.5 (c2.0, $CHCl_3$)(75%e.e.).[4]
b. Determined by hydrolysis of menthyl esters into the acids and the reported value of S-(-)β-hydroxyl β-phenyl propanoic acid: $[\alpha]_D^{17}$=-19.0 (c5.13, EtOH) (75%e.e.) [11,12].

In **Table 1**, each catalyst participated in the reaction under similar conditions, which intended to show the difference of their asymmetric catalysis abilities. The following sequence is suggested: category2, category3 > category 1. It indicates that moderate rigid structures are favorable to flexible ones. A credible explanation may be the fact that an opportune rigid ring structure of a catalyst means a less mutable conformation of its intermediate, which is one of the key points for high enantioselectivity.

Indubitably, enantioselectivity is sensitive to the ratio of the catalyst to the substrate. The higher the value within some scopes, the higher the e.e.% value is, just as described by the data in **Table 2**.

Furthermore, it is proved by the data in **Table 3** that the enantioselectivity is sensitive to the dimensional effect. The e.e.% value increases accordingly with a more bulky ester.

Finally, we feel it necessary to mention the solvent effect. All dipeptides mentioned here are almost insoluble in common organic solvents, except those that are higher polar or electron donating. Even when the mixture solvent THF-DMSO is used, it takes a long time to make the dipeptides dissolved. Poor solubility leads to limited enantioselectivity. It is one of our next aims to improve the solubility by properly modifying the peptides.

Experimental

0.1~0.5 mmol dipeptide was dissolved in 8~10 mL DMSO-THF(2:1~3:1). And then,

3 mmol benzaldehyde, 9 mmol α-bromoacetate and 9 mmol Zn-Cu couple were added one by one. After 42h reflux, the mixture was acidified (1mol/L HCl) and extracted three times (ether). The organic layer was washed (water) and dried (Na_2SO_4). After evaporation, it was purified by chromatograghy on silica gel (petroleum ether / EtOAc = 7:1 ~ 14:1) to obtain the final products.

*Ethyl β-hydroxyl β-phenyl propionate: IR (film), 3482 cm^{-1}(br, OH), 1734 cm^{-1}(C=O); ^{1}H-NMR($CDCl_3$), 1.1~1.5 (3H, t, CH_3), 2.5~2.9 (2H, d, CH_2), 3.5 (1H, br, OH), 3.9~4.4 (2H, q, OCH_2), 5.0~5.3 (1H, t, CH), 7.2~7.6 (5H,Ph).

*t-Butyl β-hydroxyl β-phenyl propionate: IR (film), 3514 cm^{-1}(br, OH), 1730 cm^{-1}(C=O); ^{1}H-NMR($CDCl_3$), 1.45 (9H, s, CMe_3), 2.47~2.68 (2H, d, CH_2), 5.07 (1H, t, CH), 7.32 (5H,Ph).

*Menthyl β-hydroxyl β-phenyl propionate: IR (film), 3414 cm^{-1}(br, OH), 1730 cm^{-1} (C=O); ^{1}H-NMR($CDCl_3$), 0.45~2.3 (17H,m), 2.69~2.76 (2H, d, CH_2), 3.39(1H, br, OH), 4.2~4.9(1H, q, $OCHR^1R^2$), 5.10 (1H, t, CH), 7.32 (5H,Ph).

Acknowledgment

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