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Asymmetric Synthesis XXV: Enantioselective Synthesis of Ethyl β -Hydroxy -β - Phenyl Propanoate via an Asymmetric Reformatsky Reaction

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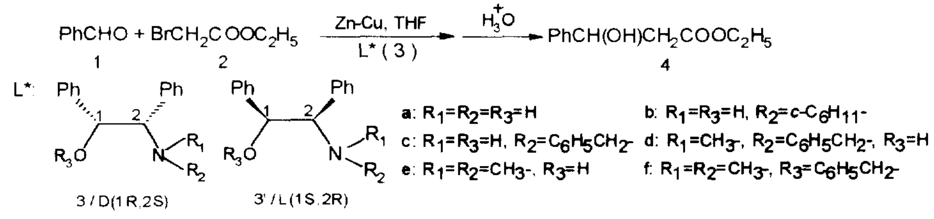
Abstract: Both stoichiometric and catalytic amounts of N,N-dialkyl derivatives of D or L-1,2-diphenyl aminoalcohols were used as chiral ligands in the enantioselective Reformatsky reaction of benzaldehyde with ethyl bromoacetate at reflux in the presence of Zn-Cu couple with e.e. up to 64%. The effects of ligand structure and solvents used on the enantioselectivity of the reaction were also studied.

The Reformatsky reaction has been investigated and applied to natural compounds.[1] Recently, Kenso Soai group[2] and Dario Pini et al[3] used stoichiometric and catalytic chiral aminoalcohols to promote the enantioselective addition of the Reformatsky reagent t-butoxycarbonylmethyl zinc bromide with a number of aromatic aldehydes at 0℃ or -20℃ with e.e.values ranging from 37% to 78% and 21% to 65% respectively. We report herein that both stoichiometric and catalytic new chiral aminoalcohols can be used in the Reformatsky reaction of benzaldehyde with ethyl bromoacetate at reflux for 5-6 h in the presence of Zn-Cu couple.(Scheme 1). In order to achieve good reactivity and enantioselectivity, several parameters were studied.



Results and Discussion

A. Selection of Chiral Ligands : With a series of chiral ligands derived from D or L-1,2-diphenyl-2-amino ethanol, the reaction results were summarized in table 1. The relationship between the amounts of chiral ligands and e.e. values was also studied.

Thus, two conclusions were drawn from the results in the table 1. Firstly, higher enantiomeric excesses were obtained using stoichiometric chiral ligands than that using catalytic amounts. A nonlinear relationship between e.e. values and the molar ratios of ligand (3'e) to benzaldehyde appeared. Secondly, it was found that the use of chiral aminoalcohols with bulky substituents on nitrogen is essential to obtain good enantioselectivity, while hydroxy groups of the aminoalcohols are necessary for enantioselectivity.

Table 1: Enantioselective Reformatsky reaction with different chiral ligands

Chiral ligands	molar ratio (ligand/PhCHO)	C.Y.[a] (%)	E.e.[b](%)	Config.[c]
3a	1.00	25.8	11.9	R
3'b	0.25	69.6	11.9	S
3c	0.25	74.7	6.8	R
3c	1.00	67.0	20.5	R
3d	0.25	64.4	27.5	R
3'd	1.00	56.7	63.9	S
3'e	0.05	85.0	7.2	S
3'e	0.25	85.0	28.2	S
3'e	0.50	82.5	39.3	S
3'e	1.00	79.8	56.9	S
3'f	0.25	59.3	0	-

a. The final products were all isolated. b. Determined by HPLC using a chiracel OD column.

c. Determined by the sign of specific rotations.[4]

.**B. Solvents Effect on the Enantioselectivity :** Sometimes solvent plays an important role in asymmetric synthesis. Table 2 listed the results in different solvents, 0.25 equimolar 3'e as chiral ligand.

Table 2: Solvents effect on the enantioselectivity

solvents	C.Y.(%)	$[\alpha]^{20}_D$ (CHCl$_3$)	E.e.(%)		Config.
acetonitrile	54.1	-10.5	19.0[a]	17.3[b]	S
THF	61.9	-12.7	23.0	23.4	S
chloroform	97.9	-5.1	9.3	8.1	S
1,2-dimethoxy ethane	59.3	-5.0	9.1	10.3	S
benzene	92.8	-3.4	6.2	6.6	S
toluene	82.5	-3.0	5.5	6.4	S

a, Calculated from specific rotation. b, Determined by chiral HPLC

From the above results, it is obvious that both donor solvent and its high polarity are essential to achive better e.e. value. The enantiomeric excess of the reaction using chloroform as a solvent is poor, because it has no effective coordinating atom despite high polarity. In reverse,1,2-dimethoxy ethane has two oxygen atoms, but its polarity is weaker, so the e.e.value of the reaction is also low. THF and acetonitrile with coordinating atom or bond and high polarity result better enantioselectivities than others.

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