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ASYMMETRIC SYNTHESES XXVI: CATALYTIC ENANTIOSELECTIVE SYNTHESES OF β -HYDROXY ESTERS VIA DOUBLE CHIRAL INDUCTION IN ASYMMETRIC REFORMATSKY REACTIONS

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Abstract: Catalytic asymmetric Reformatsky reactions of benzaldehyde with optically active menthyl bromoacetates in the presence of Zn-Cu couple were performed using 0.25 equiv. of (1*R*,2*S*) or (1*S*,2*R*)-*N*,*N*-dimethyl-2-amino-1,2-diphenyl ethanol as chiral ligand to obtain β - hydroxy esters with enantioselectivities up to 60.2%. The obvious double chiral induction effect was observed while chiral ligands matched with optically active substrates.

In the early time of 1960s, Palmer and Reid[1] used benzaldehyde to react with (-)-menthyl bromoacetate in the presence of Zn-Cu couple, and the product was hydrolyzed to *S*-(-)-β -hydroxy propionic acid with approximately 10% enantiomeric excess. Recently, Kenso Soai group[2] and Piero Salvadori research group [3] employed t-butyl bromoacetate to react with benzaldehyde induced by stoichiometric chiral amino alcohols with e.e. values up to 78% and 65%, respectively. In our preceding paper, selection of chiral ligands and solvent effect on the enantioselectivity have been reported,[4] We herein reported that 0.25 equiv.

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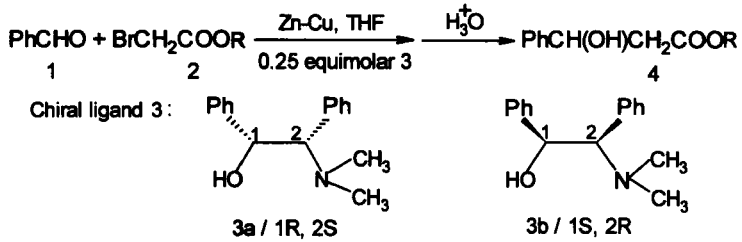
of (1*R*,2*S*) or (1*S*,2*R*)-*N*,*N*-dimethyl-2-amino-1,2-diphenyl ethanol (3) as ligand were used to the reaction of benzaldehyde with different bromoacetates. We put our emphasis on the double chiral induction system in which the reaction was not only induced by chiral ligand but also by optically active (+)-menthyl or (-)-menthyl bromoacetate (Scheme1)[5]. The enantiomeric excess of β - hydroxy esters ranged from 1.8% to 60.2% and the detailed results were listed in table 1. The absolute configuration of isopropyl, (+)-menthyl and (-)-menthyl β -hydroxy β -phenyl propionate was established by the known configuration of hydrolyzed product, β -hydroxy-β -phenyl propionic acid[6] and that of ethyl or t-butyl β -hydroxy β -phenyl propionate was determined by the sign of their standard rotations[7].



R : ethyl, iso-propyl, t-butyl, (+)-menthyl, (-)-menthyl

Scheme 1

Table 1 The results of catalytically asymmetric Reformatsky reactions

Entry	Ligand[a]	R	Yield(%)[b]	D.e.(%)[c]	Config.
1	3a	ethyl	74.7	25.1	R
2	3b	ethyl	61.9	23.4	S
3	3b	iso-propyl	57.7	36.2	S
4	3b	t-butyl	40.5	46.2[d]	S
5	/	(+)menthyl	83.6	2.5	R
6	/	(-)menthyl	83.6	1.8	S
7	3a	(+)menthyl	97.0	60.2	R
8	3a	(-)menthyl	76.3	23.9	R
9	3b	(+)menthyl	88.5	15.3	S
10	3b	(-)menthyl	73.8	54.2	S

a. The optical rotations of chiral ligand 3a and 3b are in following.

3a: $[\alpha]_D^{15}$, -8.7 (0.609, ethanol), 3b: $[\alpha]_D^{15}$, +8.1 (0.606, ethanol)

b. Isolated yield.

c. Determined by HPLC on a chiral OD column.

d. Based on the reported value, $[\alpha]_D^{22}$, -32.5 (2.0,$CHCl_3$) for 75% e.e..

From the results above, it was found that the enantioselectivities of the reaction were moderate while 0.25 equiv. of 3a or 3b was used, and e.e. values would increase accordingly with a more bulky R group of the ester (entry1-4). However, the diastereoselectivities were rather low using chiral substrate without chiral ligand(entry 5,6). What about using both chiral ligands and optically active substrates. We found that (+)-menthyl bromoacetate brought out higher e.e than (-)-menthylate using 3a as chiral ligand, On the contrary, 3b could induce higher e.e. in the reaction of (-)-menthylate than that of (+)-menthylate. It was interesting that the enantioselectivities for double chiral match system (entry 7,10) were much higher than that in single chiral system (entry 3, 4), however e.e values for double chiral mismatch system (entry 8, 9) were lower. We thought that the chirality of (+) or (-) menthylate was favorable to get higher e.e. value while it matched with the chiral ligand. On the other hand, the enantioselectivity decreased sharply while the menthylate mismatched with the chiral ligand. It was also indicated that the configuration of the products obtained was mainly controlled by the configuration of chiral ligand, not by chiral substrate. The dominated configuration of given product was depended on ligand 3a or 3b used.

Experimental

Infrared spectra were recorded on a Microlab 620MX spectrometer. ^{1}H-NMR spectra were recorded by using a Varian FT-80 and a Bruker-200 NMR spectrometer,chemical shifts were measured in ppm relative to TMS as an internal standard. The optical rotations were determined on a Perkin-Elmer 241 automatic polarimeter. The enantiomeric excesses were determined by means of HPLC with a chiralcel OD column commercially available from Daicel Chemical Industries, LTD(Japan), and isopropanol/hexane as mobile phase. Mass spectra were recorded on a VG7070E GC/MS/DS (England).

The chiral aminoalcohols were prepared by alkylation of 1,2-diphenyl amino ethanol [8]. THF was refluxed with sodium and diphenyl ketone. Benzaldehyde was distilled before using.

General precedure for asymmetric Reformatsky reaction

Chiral ligand (0.5mmol) was dissolved in 10ml THF, then adding benzaldehyde (2mmol) and ethyl bromoacetate (4mmol). The mixture was stirred

for a few minutes and Zn-Cu couple[7] (4mmol) was added, then refluxing for 5-6h. After quenching with 1N HCl aqueous and stirring for 0.5h, the mixture was extracted with ether for three times. The combined organic extracts were washed with H_2O for also three times and then dried (Na_2SO_4), evaporated under reduced pressure. The residue was purified by chromatography on silica gel (eluent: petroleum ether /EtOAc = 7:1-12:1) to get the final product 4.

ethyl β -hydroxy-β -phenyl propionate: IR (film) 3200-3600 (OH), 1740 (C=O)cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.15 (t, J=7.5Hz, 3H), 2.6 (d, J=6.2Hz, 2H), 3.25 (br,1H), 4.05 (q, J=7.5Hz, 2H), 5.0 (t, J=6.2Hz, 1H), 7.3 (m,5H)ppm. MS (m/e): 194 (M^+), 131, 107 (100%), 79.

iso-propyl β -hydroxy-β -phenyl propionate: IR (film) 3200-3600 (OH), 1735(C=O)cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.2 (d, J=6.0Hz, 6H), 2.6 (d, J=6.3Hz, 2H), 3.3 (br,1H), 4.8 (m,1H), 5.0 (t, J=6.3Hz, 1H), 7.3 (m,5H)ppm. MS (m/e): 208 (M^+), 165, 100 (100%), 77.

t-butyl β -hydroxy-β -phenyl propionate: IR (film) 3200-3600 (OH), 1730(C=O)cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.3 (s,9H), 2.6 (d, J=6.4Hz, 2H), 3.3 (br,1H), 5.0 (t, J=6.4Hz, 1H), 7.3 (m,5H)ppm. MS (m/e): 165, 107 (100%), 91, 79.

(+) or (-)-menthyl β -hydroxy-β -phenyl propionate: IR (film) 3200-3600 (OH), 1730 (C=O)cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.5-1.8 (m,18H), 2.6 (d, J=6.3Hz, 2H), 3.3 (br,1H), 4.7 (m,1H), 5.0 (t, J=6.3Hz, 1H), 7.3 (m,5H)ppm. MS (m/e): 304 (M^+), 165, 107 (100%).

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