

Asymmetric Synthesis of β -Hydroxyesters by the Enantioselective Reformatsky Reaction in the Presence of Chiral Aminoalcohols

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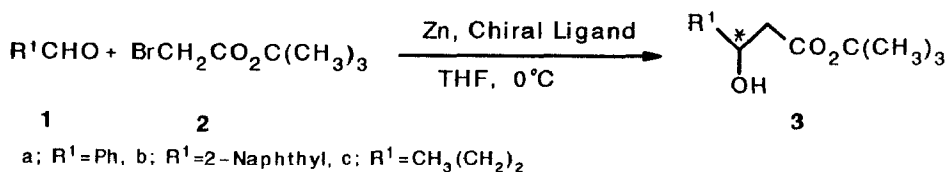
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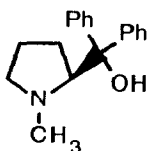
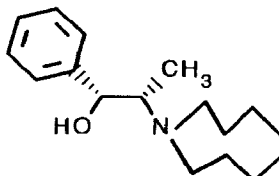
Abstract: Optically active aliphatic and aromatic β -Hydroxyesters were obtained in moderate to good enantiomeric excesses by the enantioselective Reformatsky reaction in the presence of chiral aminoalcohols.

The Reformatsky reaction affords synthetically useful β -hydroxyesters from alkyl haloacetates, zinc, and aldehydes or ketones. Its scope has been expanding, and the recent advancements in the reaction have been reviewed.¹ Although the diastereoselective Reformatsky reaction is reported (*syn/anti* selective reaction and the reaction using a covalently bonded chiral auxiliary),² to the best of our knowledge, only one report has appeared on the enantioselective Reformatsky reaction in which (-)-sparteine (chiral di-*t*-amine) is used as a chiral ligand (i.e. chiral complexing agent).³ Although the enantiomeric excess is high in one case (reaction of ethyl bromoacetate and benzaldehyde), the synthetic yield is low and the method doesn't possess generality. On the other hand, we have reported that chiral aminoalcohols are effective chiral catalysts or chiral ligands in the enantioselective additions of dialkylzincs,^{4a-d} dialkynylzincs,^{4e} difurylzinc^{4f} and organophenyl reagent^{4g} to aldehydes. However, the enantioselective reaction involving a functionalized zinc compound in the presence of a chiral aminoalcohol has not been reported.

We here report an enantioselective Reformatsky reaction using chiral aminoalcohols as chiral ligands. When benzaldehyde was reacted with the Reformatsky reagent (prepared by the reaction of *t*-butyl bromoacetate and Zn-Cu couple) in the presence of 1 mol equiv. of (*S*)-(+)-diphenyl(1-methylpyrrolidin-2-yl)methanol (**4**, DPMPM)^{4a} in THF at 0 °C, (*S*)-(-)-*t*-butyl 3-hydroxy-3-phenylpropanoate (**3a**) with 75%



Chiral Ligand

*(S)*-(+)-DPMPM(4)(1*R*,2*S*)-(+)-DBNE(5)

e.e. was obtained in 91% yield (Table, entry 1). This result shows that the Reformatsky reagent attacked from the *Si* face of the aldehyde in the presence of (*S*)-DPMPM, and that this stereochemical course is the same with that of dialkylzincs.^{4a} When 2-naphthaldehyde (**1b**) was used instead of benzaldehyde, the corresponding **3b** with 78% e.e. was obtained in 82% yield (entry 2). In addition, the reaction with butanal (**1c**, an aliphatic aldehyde) afforded aliphatic (*R*)-(-)-**3c** in 56% e.e. (entry 3). Optically active (*S*)-**3a** (44% e.e.) was also obtained when 0.4 mol equiv. of (*S*)-DPMPM(4) was employed (entry 4). As to the effect of chiral aminoalcohol, (1*R*, 2*S*)-(+)-DBNE(5) (0.4 mol equiv.) afforded (*R*)-**3a** of 37% e.e. in 89% (entry 5). It should be noted that, when the methylether of DBNE was used, the e.e. of the product was very low (1% e.e.). Thus, the hydroxy group of the aminoalcohol is important for the enantioselection.

A typical experimental procedure is as follows: (i) Preparation of the Reformatsky reagent (*t*-butoxycarbonylmethylzinc bromide): A THF solution (6 ml) of *t*-butyl bromoacetate(2)(0.432g, 6 mmol) was added to a Zn-Cu couple (Zn content 91%), and the mixture was stirred for 1 h at 90 °C. (ii) Enantioselective Reformatsky reaction: A THF solution (2 ml) of benzaldehyde (0.105g, 1 mmol) was added to (*S*)-4 (0.267g, 1 mmol) in THF (1 ml) at 0 °C and the mixture was stirred for 20 min. Then the Reformatsky reagent prepared as described above was added, and the mixture was stirred for 24 hr at 0 °C. The reaction

Table. Enantioselective Reformatsky reaction in the presence of a stoichiometric and a catalytic amount of chiral aminoalcohols (4, 5)

Entry	Aldehyde (1)	Ligand (4,5)	β -Hydroxyester(3a-c)		Yield(%)	E.e.(%)	Config.
			$[\alpha]_D$	(temp., <u>c</u> , CHCl ₃)			
1 ^a	1a	4	-32.5	(22, 2.0)	91	75 ^c	<u>S</u>
2 ^a	1b	4	-26.9	(26, 1.1)	82	78 ^d	
3 ^a	1c	4	-13.6	(24, 0.9)	60	56 ^e	<u>R</u>
4 ^b	1a	4	-19.1	(23, 1.8)	81	44	<u>S</u>
5 ^b	1a	5	+16.6	(26, 2.2)	89	37	<u>R</u>

a) Molar ratio. R¹CHO : 4 : 2 = 1 : 1 : 3. b) Molar ratio. 1a : 4 or 5 : 2 = 1 : 0.4 : 3. c) Determined by HPLC analysis of the corresponding 1-phenylpropan-1,3-diol (obtained by the reduction with LiAlH₄ using a chiral column. d) Determined by HPLC analysis using a chiral column. e) Based on the reported value of optical rotation. $[\alpha]_D$ +23.0 (c 1, CHCl₃) for 94% e.e. [R. O. Duthaler, P. Herold, W. Lottenbach, K. Oertle, and M. Riediker, *Angew. Chem. Int. Ed. Engl.*, 1989, 28, 495.]

was quenched with 1 M HCl (4 ml), and the mixture was extracted with ethyl acetate. The organic layer was dried (Na₂SO₄), and evaporated under reduced pressure. Purification by silica gel TLC (developing solvent, hexane/EtOAc = 7/2) afforded (S)-(-)-3a (0.201g) in 91% yield.

It should be noted that the enantioselective addition of β -unsubstituted chiral enolates to aldehydes has been a difficult problem.^{2b}

The present enantioselective Reformatsky reaction in the presence of chiral aminoalcohols is a convenient method for the direct preparation of optically active α -unsubstituted β -hydroxyesters in high yields.^{5,6}

References

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- 5 Recently, enantioselective synthesis of the equivalents of α -unsubstituted- β -hydroxyesters via the addition of tin enolates of thiazolidinethione and thioester of acetic acid to aldehydes have been reported. T. Mukaiyama, N. Iwasawa, R. W. Stevens, and T. Haga, *Tetrahedron*, 1984, 40, 1381; T. Mukaiyama, N. Yamasaki, R. W. Stevens, M. Murakami, *Chem. Lett.*, 1986, 213; S. Kobayashi, M. Furuya, A. Ohtsubo, and T. Mukaiyama, *Tetrahedron: Asymmetry*, 1991, 2, in press. See also, S. Masamune, T. Sato, B. Kim, and T. A. Wollmann, *J. Am. Chem. Soc.*, 1986, 108, 8279.
- 6 Partial financial support by the Chisso Award in Synthetic Organic Chemistry, Japan (to K. S.) is gratefully acknowledged.
- A Note Added in Proof: Very recently, highly enantioselective synthesis of α -unsubstituted- β -hydroxythioesters was reported from achiral silyl enol ethers and aldehydes using the catalyst system of tin(II) triflate, tributyltin fluoride, and chiral diamines. S. Kobayashi, H. Uchiro, Y. Fujishita, I. Shiina, and T. Mukaiyama, *J. Am. Chem. Soc.*, 1991, 113, 4247.