Asymmetric Addition of Reformatsky-Type Reagent to Imines Utilizing Diisopropyl Tartrate as a Chiral Auxiliary

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The asymmetric nucleophilic addition of Reformatsky-type reagent to imines, which were prepared from aldehydes and 2-aminophenols, was achieved by the use of diisopropyl (*R*,*R*)-tartrate as a chiral auxiliary to afford the corresponding β -amino acid ester derivatives with excellent enantioselectivities. In order to realize reproducible higher stereoselection, the addition of a small amount of water was crucial.

The asymmetric nucleophilic addition to a carbon–nitrogen double bond has been a focus of great attention in synthetic organic chemistry. Especially, asymmetric addition of enolates, that is Mannich-type reaction, provides an attractive route toward the optically active nitrogen-containing compounds such as β -amino acids, β -lactams, and γ -amino alcohols.¹ Although several methods of enantioselective nucleophilic addition of enolates were recently reported,^{2,3} asymmetric Mannich-type reaction is still regarded as a challenging problem in terms of enantioselectivities and the availability of chiral auxiliaries.

Recently we reported enantioselective nucleophilic addition of Reformatsky-type reagent, which was prepared in situ from diethylzinc and an iodoacetic acid ester, to 3,4-dihydroisoquinoline *N*-oxides.⁴ Herein, we wish to describe the enantioselective addition of Reformatsky-type reagent to imines, derived from aldehydes and 2-aminophenols, utilizing diisopropyl (*R*,*R*)-tartrate ((*R*,*R*)-DIPT) as a chiral auxiliary.

Firstly the enantioselective addition reaction of Reformatsky-type reagent to an imine 1a prepared from benzaldehyde and 2-aminophenol^{2a,i,5} was examined in CH₂Cl₂ at 0 °C; i.e., in the presence of a 1.0 molar amount of bis(bromomagnesium) salt 2, derived in situ from a 1.0 molar amount of (R,R)-DIPT and 2.0 molar amounts of butylmagnesium bromide (THF solution), 5.0 molar amounts of diethylzinc (hexane solution) were treated with the imine 1a followed by addition of 2.0 molar amounts of t-butyl iodoacetate. After the usual workup, the corresponding β -amino acid ester derivative **3a**⁶ was obtained in 83% yield with the enantioselectivity of 45% ee (Table 1, Entry 1). Unfortunately the enantioselectivity was not reproducible depending on the used imine 1a. A slight amount of moisture was suspected to influence on the reproducibility. When the reaction using the same imine **1a**, to which the nucleophilic addition gave 3a in 45% ee as described above, was carried out in the presence of MS 4A, the enantioselectivity was slightly decreased (Entry 2). To our surprise, the addition of water realized the enhanced enantioselectivity regardless of the used imine 1a. The influence of the amount of the added water was examined (Entries 3–10), and the highest optically active (R)- β -amino acid ester 3a was obtained with the enantioselectivity of 93% ee when 0.8 molar amount of water was added (Entry 6).



Table 1. The effect of additives in the nucleophilic addition of Reformatsky-type reagent to imine $1a^a$

Entry	Additive	n	Yield/%	ee/%b	
1			83	45	
2	MS 4A ^c		76	35	
3	H ₂ Od	0.1	71	76	
4	H ₂ Od	0.5	80	82	
5	H ₂ Od	0.7	76	92	
6	$\tilde{H_2O^d}$	0.8	77	93	
7	H ₂ Od	0.9	77	91	
8	H_2Od	1.0	73	84	
9	H ₂ Od	3.0	40	15	
10	H ₂ Od	5.0	12	0	

^aReaction times were 12–16 h. ^bOptical yields were determined by HPLC analysis (Daicel Chiralcel OD-H). ^cIn the reaction using a solution of **1a** (0.5 mmol) in CH₂Cl₂ (9 mL), 50 mg of MS 4A was added. ^dH₂O was added as a 5 mol dm⁻³ solution in THF.

The ¹H NMR spectrum of the mixture of a 1.0 molar amount of (R,R)-DIPT, 2.0 molar amounts of butylmagnesium bromide (THF- d_8 solution), 5.0 molar amounts of diethylzinc ($C_6D_5CD_3$ solution), and a 1.0 molar amount of imine **1a** in CD₂Cl₂ showed broad signals. After the addition of H₂O (THF- d_8 solution) to the solution, the peaks became rather sharp especially in the region of aromatic and methine protons originated from benzaldehyde moiety. This phenomenon might be explained as follows: The metal salts of DIPT and imine **1a** initially exist in highly aggregated form. However, after addition of H₂O, the aggregated complex was dissociated to the active form favorable to afford the higher enantioselectivity by the zinc oxide species (–ZnO–) generated from H₂O and ethylzinc reagents.^{7,8}

Next, the effect of the substituent (X) at p-position to an amino group on aromatic ring of imine was investigated. Although the nucleophilic addition to p-chloro substituted imine **1b** decreased the enantioselectivity (Table 2, Entry 2), the

introduction of methoxy group was effective to enhance the enantioselectivity up to 97% ee (Entry 3). When (*S*,*S*)-DIPT was used as a chiral auxiliary instead of (*R*,*R*)-DIPT, (*S*)-enantiomer of the product was obtained enantioselectively (Entry 4). The asymmetric addition to *p*-methoxy substituted imines **1d**–**f** was also carried out to furnish the corresponding β -amino acid esters **3d**–**f** with excellent enantioselectivity up to 98% ee (Entries 5–7).⁶



 Table 2. The asymmetric addition of Reformatsky-type reagent to imines 1 by addition of water^a

Entry		Х	R	Yield/%	ee/%	$[\alpha]_D^{25}(c, \text{EtOH})$
1	a	Н	C ₆ H ₅	77	93b	-21 (1.2)
2	b	Cl	C ₆ H ₅	76	74 ^b	-12 (1.3)
3	c	MeO	C ₆ H ₅	72	97b	-2 (1.4)
4 ^c	с	MeO	C ₆ H ₅	75	97b	+2(0.2)
5	d	MeO	PClC ₆ H ₄	80	95 ^b	+8 (1.5)
6	e	MeO	PMeOC ₆ H ₄	58	96 ^b	+11 (1.1)
7	f	MeO	^t Bu	26 ^d	98e	-12 (0.5) ^f

^aReaction times were 12–15 h. ^bOptical yields were determined by HPLC analysis (Daicel Chiralcel OD-H). $^{c}(S,S)$ -DIPT was used as a chiral auxiliary and (S)-enantiomer of the product was obtained. ^dSince the product **3f** was unstable upon the treatment in air, the product was isolated as the corresponding acetate by treating the crude product with acetic anhydride and triethylamine in the presence of p-(N,Ndimethylamino)pyridine. ^eOptical yield was determined by HPLC analysis (Daicel Chiralcel OT(+)) of the corresponding acetate of **3f**. ^fThe specific rotation of the corresponding acetate of **3f** was measured.

The absolute configuration of the compound **3c** (97% ee) was confirmed to be *R* by comparing the specific rotation of the corresponding *N*-deprotected β -amino acid ester **4** ($[\alpha]_D^{25}$ +21.4° (*c* 0.18, CHCl₃)) with that of the known (*R*)-**4** (lit.,²¹ 96% ee; $[\alpha]_D^{23}$ +22.4° (*c* 1.05, CHCl₃)). The stereochemistry of **3a** was also determined to be *R* by transformation into (*R*)-**4** [1) MeI, Na₂CO₃, 72%. 2) CAN, 39%].^{2a} The absolute configurations of **3b**,**d**–**f** were tentatively assigned to be *R*.



As described above, a new type of asymmetric Mannichtype reaction has been developed. Because of easy availability of (R,R)- and (S,S)-DIPT, the present method provides a useful way for the enantioselective synthesis of both enantiomers of β -amino acids.

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