Catalytic Asymmetric Addition Reaction of Dialkylzinc to Nitrone Utilizing Tartaric Acid Ester as a Chiral Auxiliary

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The catalytic asymmetric addition reaction of dialkylzinc to carbon-nitrogen double bond in 3,4-dihydroisoquinoline *N*-oxide derivatives was achieved by utilizing a catalytic amount of dicyclopentyl (*R,R*)-tartrate to afford the corresponding (*S*)-hydroxylamines in high optical yields up to 94% ee.

Catalytic enantioselective addition of organometallic reagents to the carbon-nitrogen double bond is one of the attractive methods for the preparation of optically active amines, which are the key intermediates for the synthesis of nitrogen-containing pharmaceutical and agrochemical substances. Although a few catalytic reactions have been reported including our original one using Chirald® as a chiral auxiliary,[1,2] these methods can be improved for practical use especially in regard of availability of chiral auxiliaries and enantioselectivity. Herein, we describe a new enantioselective addition of dialkylzinc to 3,4-dihydroisoquinoline *N*-oxide derivatives utilizing a catalytic amount of tartaric acid esters, both enantiomers of which are readily available.

First the addition reaction of diethylzinc to 3,4-dihydroisoquinoline *N*-oxide (**1a**) in the presence of 0.2 molar amounts of zinc alkoxide **2a**, derived *in situ* from diisopropyl (*R,R*)-tartrate ((*R,R*)-DIPT) and diethylzinc,[3] was examined in CH_2Cl_2 at 25 °C. As shown in the Table 1, the corresponding hydroxylamine **3a** was obtained in 61% yield, but its optical yield was disappointedly low (Entry 1). To the contrary, the bis(bromomagnesium) alkoxide **2b** was more effective to give the optically active (*S*)-hydroxylamine **3a** (Entry 2). Bromomagnesium ethylzinc alkoxide **2c** realized higher enantioselection (Entry 3). Using 2.8 molar amounts of diethylzinc, the optical yield was further improved (Entries 4, 5).

Next, the influence of the ester group in magnesium zinc alkoxide **2** (M^1=MgBr, M^2=ZnEt) was investigated.[4] The use of the esters derived from primary alcohols afforded the product **3a** with lower selectivities (Entries 7, 8). In the case of *t*-butyl ester, the enantioselectivity was also lower than that in the case of isopropyl ester (Entry 15). Esters derived from acyclic secondary alcohol, 3-pentanol, was less effective (Entry 9). Among the esters from cyclic secondary alcohols, cyclopentyl ester was found to be the ester of choice (Entries 10, 11, 13, 14). Furthermore, using methylzinc alkoxide instead of ethylzinc alkoxide, alkylation proceeded more selectively (Entries 6, 12).[5] Especially, methylzinc alkoxide **2j** derived from dicyclopentyl tartrate (DCPT) realized the highest selectivity of 82% ee.

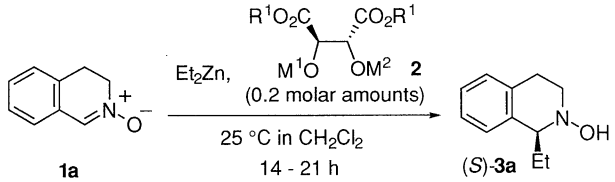


Table 1. The asymmetric addition of diethylzinc to the nitrone **1a** using the alkoxide **2** derived from (*R,R*)-tartaric acid esters

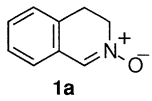
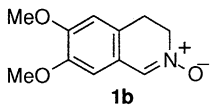
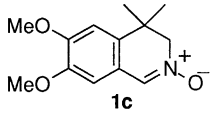
Entry	2				Et_2Zn/Molar amounts	Yield /%	ee[a] /%
	R^1	M^1	M^2				
1	isopropyl	ZnEt	ZnEt	**a**	2.0	61	3
2		MgBr	MgBr	**b**	2.0	62	43
3		MgBr	ZnEt	**c**	2.0	98	51
4		MgBr	ZnEt	**c**	2.8	98	65
5		MgBr	ZnEt	**c**	3.8	86	61
6		MgBr	ZnMe	**d**	2.8	86	72
7	methyl	MgBr	ZnEt	**e**	2.8	96	3
8	ethyl	MgBr	ZnEt	**f**	2.8	90	40
9	3-pentyl	MgBr	ZnEt	**g**	2.8	88	56
10	cyclobutyl	MgBr	ZnEt	**h**	2.8	91	51
11	cyclopentyl	MgBr	ZnEt	**i**	2.8	94	74
12		MgBr	ZnMe	**j**	2.8	89	82
13	cyclohexyl	MgBr	ZnEt	**k**	2.8	89	71
14	cycloheptyl	MgBr	ZnEt	**l**	2.8	94	71
15	*t*-butyl	MgBr	ZnEt	**m**	2.8	72	34

[a]Optical yields were determined by HPLC analysis (Daicel Chiralcel OD-H).

Then, the asymmetric addition reaction of dialkylzinc to several 3,4-dihydroisoquinoline *N*-oxide derivatives **1a-c** in the presence of bromomagnesium methylzinc alkoxide **2j** derived from (*R,R*)-DCPT was carried out. As listed in Table 2, the corresponding optically active hydroxylamines **3a-h** could be obtained with the enantioselectivity up to 94% ee.[6]

In order to investigate the role of bromomagnesium ethylzinc dialkoxide in the present reaction, the following experiments were carried out. The nitrone **1a** was treated with 1.0 molar amount of bromomagnesium ethylzinc dialkoxide **2c** derived from (*R,R*)-DIPT to give the opposite (*R*)-enantiomer **3a** with the selectivity of 62% ee, though the reaction was sluggish. When 1.0 molar amount of diethylzinc was added, (*R*)-**3a** was still preferentially obtained in 43% ee. Reversal of enantiofacial selection was observed by the addition of more than 2.0 molar amounts of diethylzinc. These results suggested that, in the catalytic reaction of diethylzinc, ethyl group predominantly transferred not from ethyl group in zinc alkoxide of tartrate (Figure 1, **A** (R^2=Et)), but from diethylzinc associated with **2** to the nitrone whose oxygen might coordinate to more Lewis acidic magnesium (Figure 1, **B** (R^2=Et)).[7,8] When methylzinc alkoxide **2d** or **2j** was used in the addition reaction of diethylzinc, only ethyl group in diethylzinc transferred resulting in the enhancement of the

Table 2. The asymmetric addition of dialkylzincs to the nitrones **1** in the presence of 0.2 molar amounts of alkoxide **2j** derived from (*R,R*)-DCPT in CH_2Cl_2 at 25 °C

Entry	Nitrones 1	R_2Zn[a]	Products 3	Yield /%	ee /%
1	 1a	Et_2Zn	a	89	82[b]
2		Me_2Zn	b	84	63[b]
3		$^nPr_2Zn$	c	85	77[b]
4	 1b	Et_2Zn	d	88	83[b]
5		Me_2Zn	e	89	64[b]
6	 1c	Et_2Zn	f	91	94[b]
7		Me_2Zn	g	95	85[b]
8		$^nPr_2Zn$	h	89	88[c]

[a]The molar amounts of dialkylzincs were 2.8. [b]Optical yields were determined by HPLC analysis (Daicel Chiralcel OD-H). [c]Optical yield was determined by ^1H NMR analysis of the corresponding (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid ester derivatives.

enantioselectivity due to the less reactivity of methylzinc moiety[7a] (Figure 1 (R^2=Me)).[9]

A typical procedure is described as follows: To a CH_2Cl_2 (3 ml) solution of (*R,R*)-DCPT (30 mg, 0.11 mmol) was added butylmagnesium bromide (0.11 mmol, 0.19 ml of 0.58 M solution in THF) at 0 °C under an argon atmosphere, and the mixture was stirred for 10 min. To the solution, dimethylzinc (0.11 mmol, 0.11 ml of 1.00 M solution in hexane) was added and the mixture was stirred for 1 h. A CH_2Cl_2 (3 ml) solution of 4,4-dimethyl-6,7-dimethoxy-3,4-dihydroisoquinoline *N*-oxide (**1c**) (108 mg, 0.53 mmol) was added followed by the addition of diethylzinc (1.48 mmol, 1.48 ml of 1.00 M solution in hexane) at 0 °C after 10 min, and the resulting solution was stirred for 19 h at 25 °C. The reaction was quenched by addition of saturated aq NH_4Cl. Purification by TLC on silica gel afforded the corresponding hydroxylamine **3f** (113 mg, 91%) with the selectivity of 94% ee.

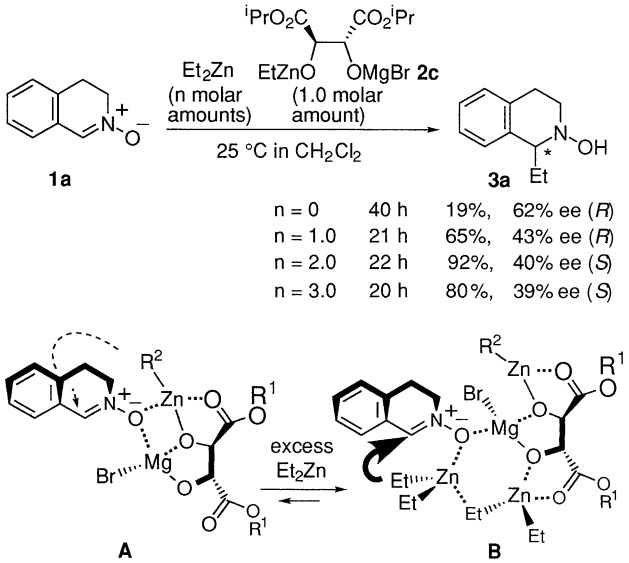


Figure 1.

As described above, the present method provides a new entry for the catalytic addition of organometallics to carbon-nitrogen double bond utilizing a catalytic amount of tartaric acid ester. Because of easy availability of (*R,R*)- and (*S,S*)-tartaric acid esters,[10,11] this method provides the useful way to prepare both enantiomers of 1-alkyl tetrahydroisoquinolines, which are the key intermediates for chiral isoquinoline alkaloids.[12]

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References and Notes

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5 In these reactions, the corresponding methylated hydroxylamine **3b** was scarcely obtained.
6 The absolute configuration of **3b** and **3e** was already confirmed.[2] The stereochemistry of other hydroxylamines was tentatively assigned by comparison of their specific rotations with those of **3b** and **3e**.
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