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Asymmetric addition of a Reformatsky-type reagent to 3,4-dihydroisoquinoline *N*-oxides

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Abstract

The asymmetric addition of a Reformatsky-type reagent, prepared in situ from diethylzinc and iodoacetic acid ester, to a carbon–nitrogen double bond in 3,4-dihydroisoquinoline *N*-oxides was achieved by utilizing diisopropyl (*R*,*R*)-tartrate as a chiral auxiliary to afford the corresponding (*S*)-1-substituted 2-hydroxy-1,2,3,4-tetrahydroisoquinolines with enantioselectivities up to 86% ee. © 2000 Elsevier Science Ltd. All rights reserved.

Chiral 1-alkyl tetrahydroisoquinolines possess important physiological properties and also serve as key intermediates for the synthesis of a variety of isoquinoline alkaloids.[1] Although diastereoselective methods for the synthesis of optically active 1-substituted tetrahydroisoquinolines have been reported,[2] enantioselective methods were still limited. For example, enantioselective reduction of 1-substituted 3,4-dihydroisoquinolines[3] and enantioselective nucleophilic addition to 3,4-dihydroisoquinoline skeletons[4,5] have been reported. We recently developed the enantioselective nucleophilic addition of dialkylzinc to 3,4-dihydroisoquinoline *N*-oxides utilizing tartaric acid ester as a chiral auxiliary.[6] If other functionalized metallic reagents in addition to dialkylzinc can be applied, this method will be more useful for the synthesis of various kinds of isoquinoline alkaloids. Among functionalized metallic reagents, enolates or their equivalents are attractive candidates. The Reformatsky-type reagent is well known as a zinc enolate equivalent.[7] Herein, we wish to describe an enantioselective addition of the Reformatsky-type reagent, prepared from diethylzinc and iodoacetic acid ester in situ,[8] to 3,4-dihydroisoquinoline *N*-oxides utilizing tartaric acid ester as an external chiral auxiliary.[9]

First, the addition reaction of the Reformatsky-type reagent derived from diethylzinc and *t*-butyl iodoacetate to 6,7-dimethoxy-3,4-dihydroisoquinoline *N*-oxide **1A** was examined (Scheme 1). That is, the nitrone **1A** was treated with a mixture of diethylzinc and *t*-butyl iodoacetate in the presence of a molar equivalent of 2-bromomagnesium 3-ethylzinc salt of tartrate, prepared in situ from diisopropyl (*R*,*R*)-tartrate ((*R*,*R*)-DIPT) and equimolar amounts of butylmagnesium bromide and diethylzinc,[6] and

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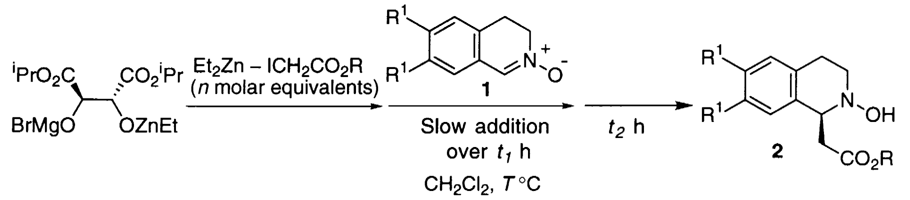
the mixture was stirred for 13 h at 25°C. As shown in Table 1, the addition reaction did not proceed using a molar equivalent of the Reformatsky-type reagent (Entry 1), but using 2 molar equivalents of the reagent, the corresponding hydroxylamine **2a** was obtained in 55% yield.[10] The enantiomeric excess of the product **2a** was determined to be 31% by HPLC analysis (Entry 2). The use of 3 molar equivalents of the Reformatsky-type reagent decreased the enantioselectivity (Entry 3). When the reaction was carried out at 0°C, **2a** was obtained with an enantioselectivity of 43% ee (Entry 4). However, the enantiofacial selection was not observed in the case of the reaction carried out at −50°C (Entry 5).



Scheme 1.

Table 1
Asymmetric addition of the Reformatsky-type reagent to nitrones **1**

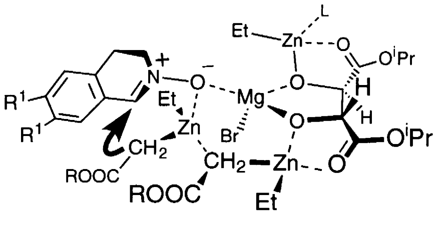
Entry	R^1	**1**	*n*	t_1(h)	t_2(h)	*T*(°C)	R	**2**	Yield/%	ee/%
1	MeO	**A**	1.0	0	13	25	*t*-Bu	**a**	trace	--
2			2.0	0	21	25			55	$31^{a)}$
3			3.0	0	17	25			39	$20^{a)}$
4			2.0	0	23	0			84	$43^{a)}$
5			2.0	0	8	-50			78	$0^{a)}$
6			1.5	2	21	0			68	$80^{a)}$
7			2.0	2	18	0			89	$82^{a,b)}$
8			3.0	2	12	0			95	$25^{a)}$
9	MeO	**A**	2.0	2	15	0	Et_3C	**b**	99	$86^{b,c)}$
10	H	**B**	2.0	2	19	0	*t*-Bu	**c**	66	$76^{b,c)}$
11	H	**B**	2.0	2	19	0	Et_3C	**d**	96	$76^{b,c)}$

a) Enantiomeric excesses were determined by HPLC analysis (Daicel Chiralcel OJ). b) $[\alpha]_D^{25}$ (EtOH) was +2 (c 5.99, Entry 7), +4 (c 1.74, Entry 9), −10 (c 0.84, Entry 10), −3 (c 1.47, Entry 11). c) Enantiomeric excesses were determined by HPLC analysis (Daicel Chiralcel OD-H).

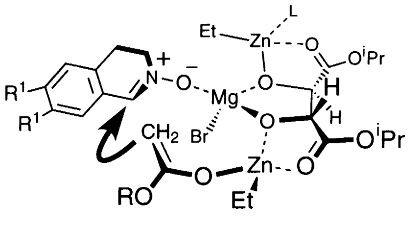
In order to improve the enantioselectivity, the slow addition of the nitrone was found to be crucial. When nitrone **1A** was slowly added to a mixture of 2-bromomagnesium 3-ethylzinc salt of (*R*,*R*)-DIPT and 2 molar equivalents of the Reformatsky-type reagent, enantioselectivity of the product **2a** was dramatically enhanced up to 82% ee (Entry 7). The slow addition method, using 1.5 and 3.0 molar equivalents of the Reformatsky-type reagent, did not improve the enantioselection (Entries 6 and 8). Finally, a higher enantioselectivity of 86% ee was realized when 1,1-diethylpropyl iodoacetate was used instead of *t*-butyl iodoacetate (Entry 9).[10]

The asymmetric nucleophilic addition to 3,4-dihydroisoquinoline *N*-oxide **1B** was also examined and similar enantioselections were observed (Entries 10 and 11).[10]

The stereochemistry of the newly formed stereogenic center in **2a** was determined to be *S*.[11] Thus, the stereochemical course of the present nucleophilic reaction was found to be the same as that for the addition of dialkylzinc to nitrone **1** utilizing (*R*,*R*)-tartaric acid ester as a chiral auxiliary reported previously.[6] Although the mechanism of the present reaction is not yet clear, 2-magnesium 3-zinc salt of DIPT seems to be present in equilibrium between a catalytically inactive highly aggregated form and a small amount of catalytically active monomer (or a lower aggregated form), probably together with a part of the Reformatsky-type reagent. Addition of the nitrone might shift the equilibrium towards dissociation of the highly aggregated form by its coordination to the catalytically active monomer. When nitrone was added all at once, only a part of the nitrone could coordinate to Lewis acidic magnesium in the monomeric salt of (*R*,*R*)-DIPT produced by dissociation. Therefore, the Reformatsky-type reagent, which was more nucleophilic than dialkylzinc, attacked not only the nitrone coordinating to the salt but also the still uncoordinated free nitrone, to afford the hydroxylamine in a less stereoselective manner. When the reaction was carried out at −50°C, the rate of dissociation was very slow and the Reformatsky-type reagent almost exclusively attacked the free nitrone without enantioselection. However, the nitrone effectively coordinated to the dissociated salt of (*R*,*R*)-DIPT by the slow addition method to produce the hydroxylamine enantioselectively through a transition state such as T_1 or T_2, shown below.[6,12]



T_1



T_2

As described above, the Reformatsky-type reagent, generated in situ from diethylzinc and iodoacetic acid ester, was found to be an attractive nucleophile in the enantioselective addition to 3,4-dihydroisoquinoline *N*-oxides. Because of easy availability of (*R*,*R*)- and (*S*,*S*)-DIPT, this method provides a useful way to prepare both enantiomers of 1-substituted tetrahydroisoquinolines, which are the versatile intermediates for the synthesis of chiral isoquinoline alkaloids.

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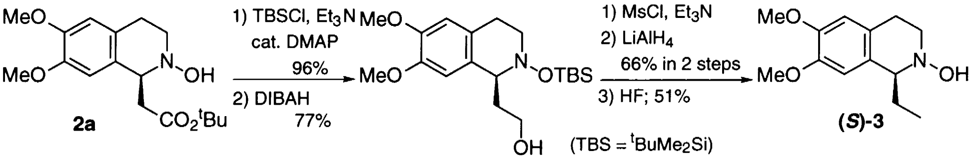
11. According to the following scheme, the product **2a** (60% ee) was transformed to the known compound (*S*)-**3** whose absolute configuration is unambiguous.[6,13] (*S*)-**3**: $[\alpha]_D^{25}$ −31 (*c* 0.06, MeOH); lit.[13] (*R*)-**3** (65% ee): $[\alpha]_D^{25}$ +33 (*c* 1.00, MeOH).



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