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Control of Enantiofacial Differentiation in the Addition Reaction of Organometallics to a Nitrone in the Presence of an External Chiral Auxiliary

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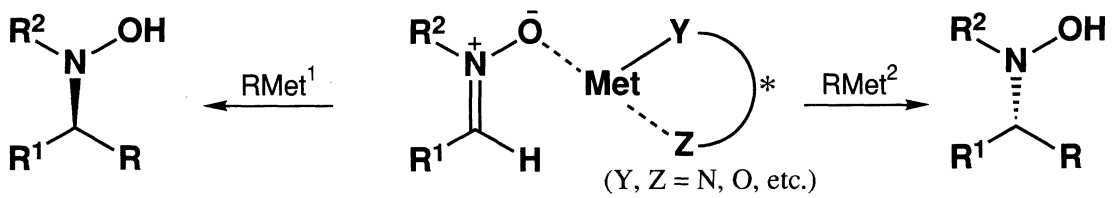
It was observed that differentiation of enantiotopic face in the addition reaction of organometallics to 3,4-dihydroisoquinoline *N*-oxide was well-regulated by the use of an external chiral auxiliary; *i.e.*, Grignard reagents added from the *si*-face of the nitrone in the presence of bromomagnesium (*2S,3R*)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butoxide, while dialkylzinc attacked from the *re*-face.

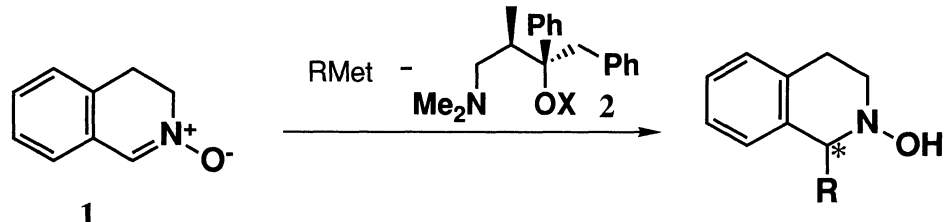
The asymmetric carbon-carbon bond formation in the addition reaction of organometallic reagents to the imine and its derivatives constitutes an attractive method for the preparation of optically active amines. Although the impressive progress has been made in the asymmetric addition of organometallics to carbonyl compounds using external chiral auxiliaries,[1] examples of the asymmetric addition of organometallic reagents to imine functions are still limited.[2,3] In this paper, we report a new approach for the preparation of optically active amines by the use of an external chiral auxiliary.

It has already been reported that the stereochemical course of nucleophilic addition reaction of organometallics to chiral imines, in which the imine function is directly connected to the chiral inducing moiety possessing a hetero atom by the covalent bond, can be controlled by the appropriate selection of the metal.[4] For the higher efficiency in asymmetric carbon-carbon bond formation, it was strongly desired to prepare both enantiomers of amines from an achiral imine using an external auxiliary. When imine function was strongly bridged with chiral inducing moiety possessing hetero atoms by coordinate bond of metal, enantiofacial differentiation in the nucleophilic reaction of organometallics would be possible by the use of the appropriately selected metals (Scheme 1). Among the imine functions, nitrone might be suitable for the substrate because it possesses an electronegative oxygen which could strongly coordinate to metals.[5] Based on this hypothesis, 3,4-dihydroisoquinoline *N*-oxide[6] (**1**) was chosen as a substrate,[7] and the nucleophilic addition reaction was investigated using the metal alkoxide derived from (*2S,3R*)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol (Chirald®) (**2**, X = H) as a chiral auxiliary: the results are shown in Table 1.

Firstly, the addition reaction of ethyl metallic reagents to the nitrone **1** was examined. EtMgCl (2.2 equiv.)



Scheme 1.



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3 **a**; R = Et
b; R = Me

Table 1. The addition reaction of organometallics to the nitrone **1**

Entry	RMet	X in **2**	Additive	Solvent[a]	Temp	Products	Yield/%[b]	ee/%[c]
1	EtMgCl[d]	MgCl	---	THF	-78 °C - rt	**3a**	65 (90)	43(*S*)
2	EtMgBr[d]	MgBr	---	THF	-78 °C - rt		67 (95)	52(*S*)
3			---	toluene	-78 °C - rt		60 (97)	61(*S*)
4			---	Et_2O	-78 °C - rt		54 (84)	75(*S*)
5			---	DME	-78 °C - rt		52 (77)	54(*S*)
6	EtMgI[e]	MgI	---	THF	-78 °C - rt		84 (91)	50(*S*)
7	EtMgCl[d]	MgCl	$MgCl_2$	THF	-78 °C - rt		78 (99)	43(*S*)
8	EtMgBr[d]	MgBr	$MgBr_2$	THF	-78 °C - rt		42 (81)	71(*S*)
9			$MgBr_2$	toluene[f]	-78 °C - rt		52 (83)	78(*S*)
10			$MgBr_2$	Et_2O[f]	-78 °C - rt		26 (99)	77(*S*)
11			$MgBr_2$	DME[f]	-78 °C - rt		33 (54)	90(*S*)[g]
12			$MgBr_2$	DME[f]	-45 - -38 °C		54 (78)	81(*S*)
13	Et_2Zn[h]	MgBr	---	THF	-78 °C - rt		25 (36)	44(*R*)
14			---	toluene	-78 °C - rt		32 (40)	37(*R*)
15			---	Et_2O	-78 °C - rt		36 (73)	48(*R*)
16			---	DME	-78 °C - rt		35 (47)	37(*R*)
17	Et_2Zn[h,i]	MgBr	---	THF	-20 °C		54 (81)	33(*R*)
18			---	THF	0 °C		91 (95)	44(*R*)
19			---	THF	25 °C		74 (81)	57(*R*)[g]
20	MeMgBr[d]	MgBr	$MgBr_2$	THF	-78 - -35°C	**3b**	41 (99)	80(*S*)[g]
21			$MgBr_2$	DME[f]	-78 °C - rt		40 (70)	60(*S*)
22	Me_2Zn[h,i]	MgBr	---	THF	0 °C		79 (87)	50(*R*)
23			---	THF	25 °C		88 (99)	66(*R*)[g]

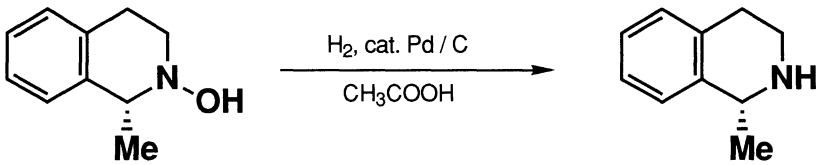
a) In all cases, the solvent which came from organometallics' stock solution was present in the reaction mixture (*ca.* 10% v/v). b) The yields in parentheses are based upon conversion. c) Optical yields were determined by HPLC analysis (Daicel Chiralcel OD-H, hexane-EtOH-Et_2NH (200 : 1 : 4)) and/or, in the case of **3a**, by the conversion to the corresponding acetate of **3a** followed by ^1H NMR analysis in the presence of $Eu(hfc)_3$. d) Grignard reagent stocked in THF was used. e) Grignard reagent stocked in Et_2O was used. f) In the reaction mixture, THF used for the preparation of $MgBr_2$ was present (*ca.* 30% v/v). g) $[\alpha]_D^{25}$ (MeOH) was -59° (c 0.31; Entry 11), +39° (c 0.72; Entry 19), -48° (c 0.13; Entry 20), and +43° (c 0.49; Entry 23). h) Dialkylzinc stocked in hexane was used. i) 2.2 Equiv. of dialkylzinc were used.

was treated with Chirald® (1.1 equiv.) to generate magnesium alkoxide **2** (X = MgCl) (1.1 equiv.), and the nitrone **1** (1.0 equiv.) was subsequently added to the solution at -78 °C. The reaction mixture was gradually warmed to room temperature spending overnight and then treated with saturated aq NH_4Cl. After the purification of the crude product by TLC on silica gel, the alkylated product (*S*)-**3a** was obtained in 65% yield and 28% of the unreacted **1** was recovered. The enantiomeric excess was determined to be 43% by HPLC analysis (Entry 1). The reaction using EtMgBr or EtMgI in the presence of magnesium alkoxide **2** (X = MgBr or MgI, respectively), slightly enhanced the stereoselectivity (Entries 2 or 6). The influence of the solvents was examined (Entries 2 - 5), and in Et_2O the product was obtained in 75% ee. After several attempts to improve the enantioselectivity, addition of $MgBr_2$ (1.1 equiv.), generated from Mg and 1,2-dibromoethane in THF *in situ*, was found to be effective, while $MgCl_2$ was ineffective (Entries 7 and 8). In most of the solvents used, such as THF, toluene, and Et_2O, the stereoselectivity was enhanced (Entries 8 - 10) by the addition of $MgBr_2$ and, especially in DME, high stereoselectivity up to 90% ee was realized (Entry 11). When the reaction was carried out in DME at around -40 °C, (*S*)-**3a** was produced in 54% yield with enantioselectivity of 81% ee (Entry 12).

In contrast, the reverse enantioselectivity was observed when Et_2Zn was used as an organometallic reagent in the presence of magnesium alkoxide of Chirald® **2** (X= MgBr). The nitrone **1** (1.0 equiv.) was added to the mixture of Chirald® (1.1 equiv.) and EtMgBr (1.1 equiv.), followed by the treatment with Et_2Zn (1.1 equiv.). After the usual workup, (*R*)-**3a** was mainly obtained. In the reaction using Et_2Zn, solvent influenced the selectivity only little (Entries 13 -16). When 2.2 equiv. of Et_2Zn were used, the yield was enhanced. Interestingly, at the higher reaction temperature, the higher enantioselectivity was found (Entries 17 - 19).[8]

Next, the reaction of methylmetallic reagents with the nitrone **1** was examined using magnesium alkoxide **2** (X= MgBr) as a chiral auxiliary, and the same tendency as above was observed in stereochemical course; *i.e.*, MeMgBr in the presence of $MgBr_2$ afforded the (*S*)-**3b**, while (*R*)-**3b** was preferentially obtained by the reaction with Me_2Zn. In the reaction with MeMgBr, higher selectivity was realized in THF than in DME (Entries 20 and 21), and the similar temperature effect was also observed in the reaction with Me_2Zn (Entries 22 and 23).

The stereochemistry of the newly formed chiral center in the (*R*)-**3b** was determined by conversion to the optically active amine **4**; *i.e.*, hydrogenation[6] of the product (50% ee) from the reaction of **1** with Me_2Zn gave the optically active amine **4** ($[\alpha]_D^{25}$ +39° (c 0.37, THF)) in 75% yield, whose configuration was confirmed to be *R* by the comparison with the reported specific rotation of (*S*)-**4** ($[\alpha]_D^{25}$ -71.3° (c 0.64, THF)).[9]



(*R*)-**3b** (*R*)-**4**

Although the precise mechanism is still an open question, the stereochemical course might be explained as follows: In the reaction of Grignard reagent to the nitrone **1**, which is coordinated to magnesium alkoxide of Chirald®, Grignard reagent would be aggregated through the bridging bromide ion as depicted in Fig. 1 (X = R) based on molecular models, and the alkyl group predominantly transferred from the *si*-face of the nitrone **1**. In the presence of $MgBr_2$, which would be coordinated the oxygen of the nitrone **1**, Grignard reagent could be rigidly aggregated and would attack more selectively from the *si*-face (Fig. 1, X = Br). On the other hand, dialkylzinc could not be aggregated with magnesium alkoxide of Chirald® and would approach from the less hindered *re*-face (Fig. 2).

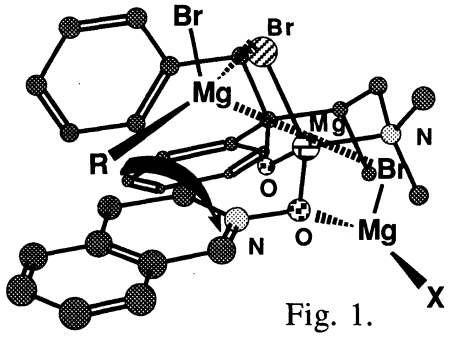


Fig. 1.

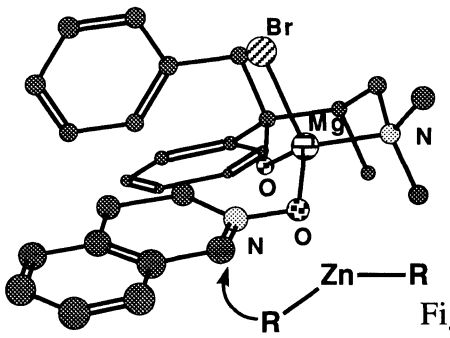


Fig. 2.

As described above, the present method appears quite promising for the stereoselective preparation of both enantiomers of amines starting from an achiral substrate by the judicious choice of organometallics in the presence of an external chiral auxiliary. Furthermore, it also offers a useful way for the synthesis of chiral 1-alkyltetrahydroisoquinolines, which are the key intermediates for chiral isoquinoline alkaloids.[10]

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