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Reversal of Diastereofacial Selectivity in the Addition Reaction of Organometallics to Chiral Imines

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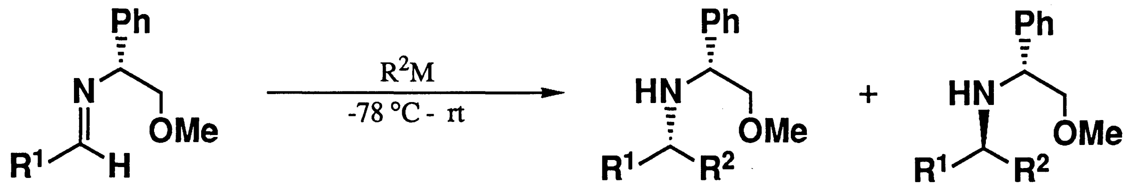
It was observed that diastereofacial selectivity in the addition reaction of organometallics to the chiral imines derived from (*R*)-2-methoxy-1-phenylethylamine was regulated under appropriate conditions; *i. e.*, organolithium and organocerium reagents added from the *re*-face of the chiral imines selectively, while organocopper reagents attacked from the *si*-face. The utility of the present method was demonstrated in the enantioselective synthesis of solenopsin A.

The asymmetric carbon-carbon bond formation in the addition reaction of organometallic reagents to an imine and its derivatives offers an attractive approach for the preparation of optically active amines. Although impressive progress has been made recently,[1,2] these reactions are limited to the formation of amines in only one enantiomer because the employed chiral auxiliaries from naturally occurring compounds such as amino acids are not always available for both enantiomers. Being concerned with this problem, we have studied the diastereofacial differentiating reaction of organometallics to chiral oxime ethers.[3] In this paper, we report a new approach for the preparation of both enantiomers of amines from a single starting material by the appropriately selected organometallics.

Introduction of the hetero atom, which could coordinate on a metal, into the chiral auxiliary of the imine might furnish the alterable coordination states by the interaction between organometallics depending on the kind of metal used. By this hypothesis, (*R*)-2-methoxy-1-phenethylamine,[4] which possesses an ethereal oxygen, was chosen as a chiral auxiliary. The chiral imines **1** were prepared by the condensation of the corresponding aldehydes and the chiral amine in the presence of MS 4A and the crude **1** was used for the subsequent reaction without further purification. First, the addition reaction of the chiral imine **1A** with MeLi in diethyl ether was examined. After hydrolysis of the reaction mixture followed by extraction and purification by TLC on silica gel,



1 **(*R*,*R*)-2** **(*R*,*S*)-2**

A; R^1 = $PhCH_2CH_2$
B; R^1 = Ph
C; R^1 = n-$C_{11}H_{23}$ C_3H_6 (≡R*)

a; R^1 = $PhCH_2CH_2$ R^2 = Me
b; R^1 = $PhCH_2CH_2$ R^2 = n-Bu
c; R^1 = Ph R^2 = Me
d; R^1 = R* R^2 = Me

Table 1. The addition reaction of organometallics to the chiral imines **1**.

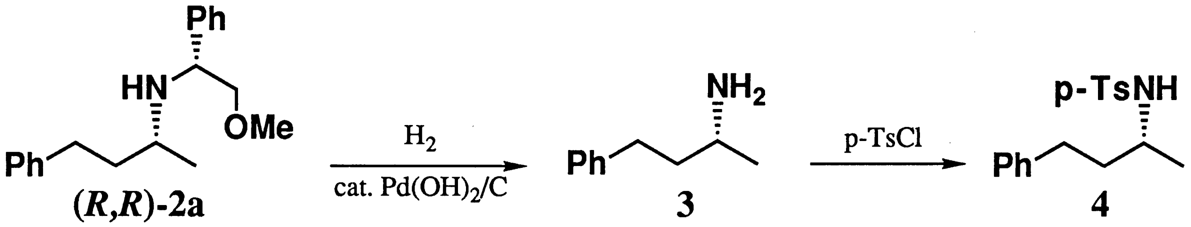
Entry	**1**	R^1	R^{2}M	(equiv.)	Solvent	Products	Yield/%	(R,R)-**2** : (R,S)-**2**
1	**A**	PhCH$_2$CH$_2$	MeLi	(1.2)	Et$_2$O	**a**	53	99 : 1 a)
2			MeCeCl$_2$	(1.2)	THF		55	98 : 2 a)
3			MeCu·BF$_3$ b)	(5)	THF		42	35 : 65 a)
4			MeCu·BF$_3$ c)	(1.3)	Et$_2$O		9	14 : 86 a)
5			Me$_2$CuLi·BF$_3$ c)	(1.2)	THF		27	2 : 98 a)
6			Me$_2$CuLi·BF$_3$ c)	(5)	THF		54	3 : 97 a)
7	**A**	PhCH$_2$CH$_2$	n-BuLi	(1.2)	Et$_2$O	**b**	45	97 : 3 d)
8			n-BuCeCl$_2$	(1.6)	THF		61	>97 : <3 d)
9			n-Bu$_2$CuLi·BF$_3$ c)	(1.2)	THF		23	8 : 92 d)
10			n-Bu$_2$CuLi·BF$_3$ c)	(5)	THF		51	18 : 82 d)
11			n-Bu$_2$CuLi·BF$_3$ e)	(5)	THF		54	13 : 87 d)
12	**B**	Ph	MeLi	(1.5)	Et$_2$O	**c**	73	>99 : <1 a)
13			MeCu·BF$_3$ b)	(5)	THF		43	12 : 88 a)
14			Me$_2$CuLi·BF$_3$ c)	(5)	THF		14	7 : 93 a)
15	**C**	R*	MeLi	(5)	Et$_2$O	**d**	66	95 : 5 f)
16			MeCeCl$_2$	(4)	THF		65	97 : 3 f)
17			Me$_2$CuLi·BF$_3$ c)	(5)	THF		52	14 : 86 f)
18			Me$_2$CuLi·BF$_3$ e)	(5)	THF		56	10 : 90 f)

a) The ratio was determined by capillary GLC (SE-30). b) The copper reagent was prepared from MeMgBr and CuI. c) The copper reagent was prepared from R^{2}Li and CuI. d) The ratio was determined by ^{13}C NMR spectrum. e) The copper reagent was prepared from R^{2}Li and CuBr·Me$_2$S. f) The ratio was determined by ^{1}H NMR (270 MHz) spectrum.

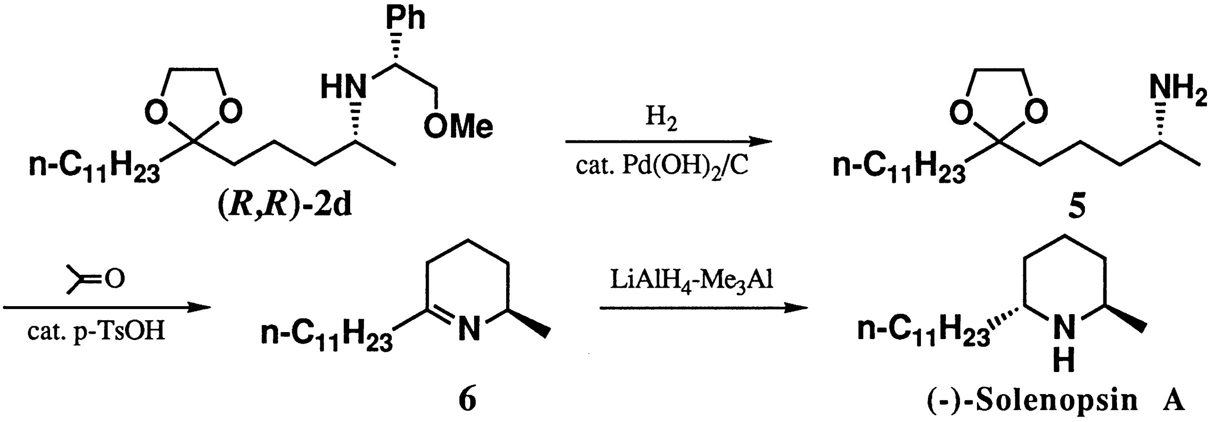
(R)-N-((R)-2-methoxy-1-phenylethyl)-1-methyl-3-phenylpropylamine was selectively obtained in 53% yield. As shown in the Table 1, the diastereomeric ratio was determined to be 99 : 1 by capillary GLC analysis (Entry 1). The addition of MeCeCl$_2$, prepared from MeLi and CeCl$_3$ *in situ*,[5] also occurred from the *re*-face of the imine **1A** in a highly stereoselective manner (Entry 2). In contrast, the changeover in diastereoselectivity was observed using BF$_3$ complexes of methylcopper reagents.[6,7] Especially, the use of Me$_2$CuLi·BF$_3$ attained high stereoselectivity for the *si*-facial attack (Entry 5) and the use of a 5 molar amount of the reagent enhanced the yield (Entry 6).

In the addition reaction of **1B** and **1C**, a similar tendency was observed in the stereochemical course ; *i. e.*, organolithium and cerium reagents afforded the corresponding (R,R)-amines with high selectivity, while the (R,S)-amines were preferentially produced by the reaction with organocopper reagents, in which the yields and the selectivities were little influenced by the reaction conditions. In the reaction of the imine **1A** with n-Bu$_2$CuLi·BF$_3$, using excess amounts of reagents decreased the selectivity (Entry 10), whereas the copper reagents prepared from CuBr·Me$_2$S again enhanced the selectivity (Entry 11). The chiral imine **1B** derived from benzaldehyde was less reactive to Me$_2$CuLi·BF$_3$ (Entry 14). Furthermore, the ketal oxygen of the imine **1C** scarcely affected the stereochemical course (Entries 15 - 18).

The stereochemistry of the newly formed chiral center in the adducts (R,R)-**2a** was determined by the conversion to an optically active sulfonamide **4**; *i. e.*, the hydrogenation of (*R*,*R*)-**2a** from the reaction of **1A** with $MeCeCl_2$ gave an optically active amine **3** by the removal of chiral auxiliary and the successive treatment with *p*-toluenesulfonyl chloride provided the sulfonamide **4** ($[\alpha]_D^{23}$ +28°, $[M]_D^{23}$ +83° (c 1.7, EtOH)), whose configuration was confirmed to be *R* by comparison of its specific rotation with the reported one of (*S*)-**4** (lit.,8) $[M]_D^{21}$ -86° (10.2% EtOH)). The chemical shifts of (*R*,*R*)-**2c** and (*R*,*S*)-**2c** were well agreed with the reported data.1d) Further, the configuration of (*R*,*R*)-**2d** and (*R*,*S*)-**2d** was assigned by the similarity of their chemical shifts of methyl protons to those in (*R*,*R*)-**2a**, (*R*,*S*)-**2a** and (*R*,*R*)-**2c**, (*R*,*S*)-**2c**, respectively; *i. e.*, methyl protons of (*R*,*R*)-isomers appear at lower fields than those of (*R*,*S*)-isomers.

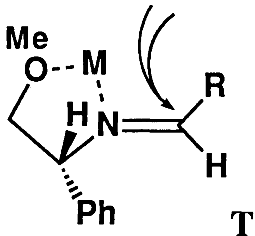


In order to demonstrate the usefulness of the present method, the synthesis of (-)-solenopsin A was performed. The 2,6-*trans*-dialkylpiperidine derivative solenopsin A is the major saturated component of a closely related family of alkaloids isolated from the venom of fire ant, *Solenopsis saevissima,* and exhibits pronounced hemolytic, insecticidal and antibiotic activities.9, 10) Hydrogenation of (*R*,*R*)-**2d** gave an amine **5** (quant.), which was optically purified by recrystallization. The cleavage of an acetal linkage in **5** with a catalytic amount of *p*-TsOH in acetone yielded the cyclic imine **6**, which was successively treated with $LiAlH_4$-Me_3Al11) afforded (-)-solenopsin A (49% from **5**, $[\alpha]_D^{23}$ -2.2° (c 0.8, MeOH), HCl salt $[\alpha]_D^{23}$ -7.6° (c 0.7, $CHCl_3$); lit.12a) (2*S*, 6*S*), $[\alpha]_D^{20}$ +7.5° (c 1.3, $CHCl_3$)) and the corresponding *cis*-isomer isosolenopsin A (15%) ($[\alpha]_D^{23}$ -4.6° (c 0.3, MeOH)).12)



Although the precise mechanism of the present reaction is still an open question, the stereoselection might be explained in terms of a chelation-controlled model and an open-chain model; *i. e.*, lithium and cerium reagents would be coordinated by the nitrogen and oxygen atoms of the imine and the attack of the alkyl group might occur from the less hindered side to give the (*R*,*R*)-isomer (T_1). In the reaction with copper reagents, on the other hand, the simultaneous chelation of two hetero atoms to the metal would not occur and the reaction might proceed through the open-chain transition state to afford the (*R*,*S*)-product (T_2).1c, g)

As described above, the present method provides a useful way for the stereoselective preparation of both enantiomers of amines starting from a single substrate by the judicious choice of organometallics.



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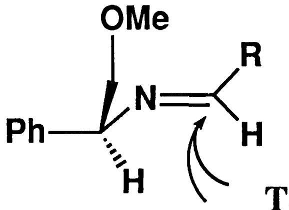

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