Stereoselective Addition Reaction of Organolithium Reagents to Chiral Imines Derived from *erythro*-2-Amino-1,2-diphenylethanol

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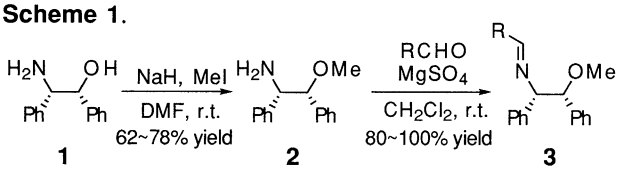
The chiral imines prepared from an artificial chiral auxiliary, *erythro*-2-amino-1,2-diphenylethanol, and various aldehydes, reacted with organolithium reagents to give the corresponding chiral amines with excellent diastereofacial selectivity.

In asymmetric syntheses, a number of chiral auxiliaries have been developed and enabled us to prepare desired compounds in high stereoselectivity. However, many of these chiral auxiliaries are based on naturally occurring compounds and then only one enantiomer can practically be available. In our study on the optical resolution of artificial racemates,[1,2] we have achieved to resolve *erythro*-2-amino-1,2-diphenylethanol (**1**) by preferential crystallization,[1] which preparatively gives both enantiomers by simple operation. Utilizing this artificial chiral auxiliary in asymmetric syntheses, each enantiomer of a desired compound would be easily prepared. As one of the applications of artificial chiral auxiliary **1** to asymmetric syntheses, we reported that chiral imines of cyclohexanone with *erythro*-2-methoxy-1,2-diphenylethylamine (**2**), which can be easily prepared by *O*-methylation of **1**, was successfully alkylated via their metalloenamines and gave both enantiomers of 2-alkylcyclohexanones in good stereoselectivity.[3] In this report, we wish to describe the diastereofacially selective addition reactions of organometallic reagents to chiral imines **3** derived form **2** and various aldehydes (Scheme 1).[4,5]

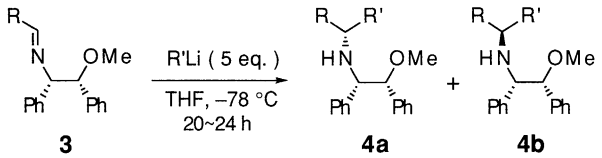
Scheme 1.



1 **2** **3**

At first, we examined alkylation reaction of various chiral imines **3** with alkyllithium reagents (Table 1). In all cases, excellent diastereofacial selectivity was observed. Relative stereochemistry of the major product **4a** was determined by X-ray crystallography after derivatization to hydrochloride salt of the product for Entry 1[6] or by the comparison of its GC and NMR with those of the products for the other entries. When a α,β-unsaturated imine was used (Entry 5), the reaction regioselectively proceeded in a 1,2-addition manner. An enolizable imine bearing α-proton (Entry 6) was also alkylated without serious decrease in the chemical yield. These successful results encouraged us to apply this reaction strategy to synthetically more valuable reaction such as allylation reaction (Table 2).[7]

As the alkylation reaction mentioned above, allyllithium reagent provided corresponding homoallylamine **6a** in excellent diastereofacial selectivity (Entry 1). In crotylation reaction, no stereoselectivity was observed under Lewis acidic conditions (Entry 2), and the reaction hardly proceeded by Cr or Si reagent, which is known as a selective crotylation reagent (Entries 3,4).[7] On the other hand, by the reaction with crotylmagnesium reagent (Entry 5), corresponding homoallylamine **6a** was obtained in



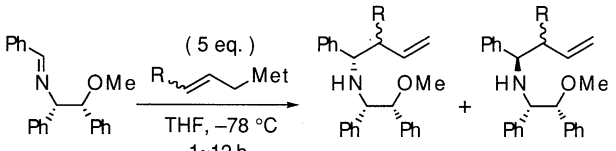
3 **4a** **4b**

Table 1. Nucleophilic Addition of Alkyllithium Reagents to Chiral Imines **3**

Entry	R	R'	Yield / %	**4a**:**4b**[c]
1[a]	Ph	Me	89	99:1
2[b]		^{n}Bu	64	99:1
3	p-ClC$_6$H$_4$	Me	69	99:1
4	p-MeOC$_6$H$_4$		60	94:6
5	PhCH=CH		43	98:2
6	^{i}Pr	Ph	50	99:1

[a]Reaction temperature: r.t. [b]Reaction temperature: –78 °C~r.t. [c]Determined by GC.

excellent diastereofacial selectivity, but the *erythro*/*threo* selectivity was not satisfactory. In the case of crotyllithium reagent (Entry 6), excellent diastereofacial selectivity and moderate *erythro*/*threo* selectivity were observed, but α-adduct



5 **6a** **6b**

Table 2. Nucleophilic Addition of Allylmetallic Reagents to Chiral Imine **5**

Entry	R	Metal	Yield / %[c]	**6a**:**6b**[d]	*Erythro* :*threo* of **6a**[e]
1	H	Li	80	99:1	–
2[a,b]	Me	$SnBu_3$ / $BF_3{\cdot}OEt_2$	48	50:50	42:58
3[a,b]		SiF_3 / CsF	0	–	–
4[a]		CrBrCl	0	–	–
5		MgCl	90	100:0	64:36
6		Li	72[f]	100:0	84:16

[a]Reaction temperature: –78 °C~r.t. [b]Solvent: CH_2Cl_2. [c]Yield of a mixture of **6a** and **6b**. [d]Determined by GC. [e]Relative stereochemistry was not determined. [f]α-Adduct was formed in 18% yield.

was formed in 18% yield as a by-product. Further efforts to improve the *erythro/threo* and α/γ selectivity by investigating a solvent and an additive gave no positive effect. Then, allylation reactions were performed by using allylic lithium reagents, and the results are summarized in Table 3.

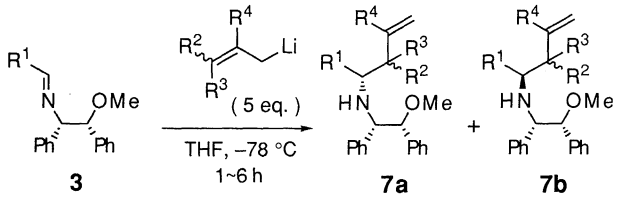


Table 3. Nucleophilic Addition of Allyllithium Reagents to Chiral Imines **3**

Entry	R^1	R^2	R^3	R^4	Yield / %[a]	**7a**:**7b**[b]
1	Ph	H	H	H	80	99:1
2		Me	H	H	72[c]	100 (84:16[e]):0
3		Me	Me	H	75[d]	97:3
4		H	H	Me	68	100:0
5	PhCH=CH	H	H	H	57	96:4
6	^{i}Pr	H	H	H	50	99:1

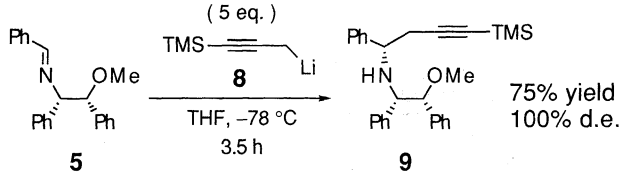
[a]Yield of a mixture of **7a** and **7b**. [b]Determined by GC. [c]α-Adduct was formed in 18% yield. [d]α-Adduct was not detected. [e]*Erythro:threo* ratio of **7a**. Relative stereochemistry was not determined.

In all cases, excellent diastereofacial selectivity was observed. Similar to the alkylation reactions, the α,β-unsaturated imine was regioselectively allylated in a 1,2-addition manner (Entry 5) and the reaction of the enolizable imine proceeded without serious decrease in chemical yield (Entry 6).

A representative procedure for the synthesis of chiral homoallylamines is as follows. To a stirred solution of 2-butenyltriphenyltin (855 mg, 2.11 mmol) in anhydrous THF (8 ml) was added phenyllithium (1.13 ml, 2.03 mmol; 1.8 M cyclohexane/ether solution) at an ambient temperature under an argon atmosphere. After white precipitate was formed, the solution was further stirred for 30 min. To this solution was added benzaldimine **5** (99.1 mg, 0.314 mmol) in THF (5 ml) at −78 °C. At the same temperature the solution was stirred for 1 h, and then saturated aqueous ammonium chloride (5 ml) was added to the reaction mixture. Following the usual workup procedure, the corresponding homoallylamine (84.1 mg, 0.226 mmol, 72%) and α-adduct (21.6 mg, 0.0581 mmol, 18%) were obtained.

In addition to allylation reactions, propargyllithium reagent **8** also reacted with chiral imine **5**[4c] to give homopropargylamine **9**

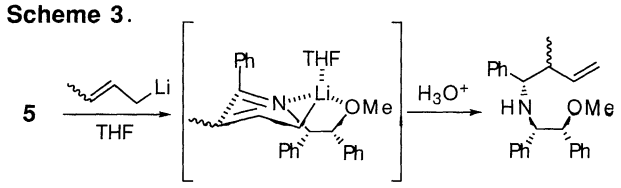
Scheme 2.



in excellent diastereofacial- and regio-selectivity. Regioisomer, homoallenylamine, was not detected at all.

Diastereoselectivity of the reaction was explained by the transition state model in Scheme 3. In allylation reaction, a rigid fused 5-6 membered ring is expected to be formed by the chelation between Li cation and the ether oxygen of the chiral auxiliary, and the two phenyl groups of the chiral auxiliary are arranged to the one side of the diastereofaces of the imine. Therefore, the direction of nucleophilic attack to the imine is strongly restricted to the opposite side of the phenyl groups to give excellent diastereofacial selectivity.

Scheme 3.



In conclusion, we succeeded in developing a highly diastereoselective addition reaction of organolithium reagents to chiral imines derived from an artificial chiral auxiliary. This procedure would be a useful method for the preparation of both enantiomers of chiral amines.

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References and Notes

1 K. Saigo, S. Ogawa, S. Kikuchi, A. Kasahara, and H. Nohira, *Bull. Chem. Soc. Jpn.*, **55**, 1568 (1982).

2 A. Sudo, Y. Hashimoto, H. Kimoto, K. Hayashi, and K. Saigo, *Tetrahedron Asym.*, **5**, 1333 (1994); K. Sakai, Y. Hashimoto, K. Kinbara, K. Saigo, H. Murakami, and H. Nohira, *Bull. Chem. Soc. Jpn.*, **66**, 3414 (1993); K. Saigo, I. Sugiura, I. Shida, K. Tachibana, and M. Hasegawa, *Bull. Chem. Soc. Jpn.*, **59**, 2915 (1986).

3 K. Saigo, A. Kasahara, S. Ogawa, and H. Nohira, *Tetrahedron Lett.*, **24**, 511 (1983).

4 (a) Y. Ukaji, T. Watai, T. Sumi, and T. Fujisawa, *Chem. Lett.*, **1991**, 1555; (b) Y. Suzuki and H. Takahashi, *Chem. Pharm. Bull.*, **31**, 2895 (1983); (c) For a review on reaction of allyl- and propargylmetallics with imines, see: E. F. Kleinman and R. A. Volkmann, In *Compreh. Org. Synth.*; C. H. Heathcock, Ed.; Pergamon: Oxford (1990); Vol. 2, p. 975.

5 For a recent report on the asymmetric addition reaction of organometallics to achiral imines in the presence of chiral ligands, see: E. S. Denmark, N. Nakajima, and O. J.-C. Nicaise, *J. Am. Chem. Soc.*, **116**, 8797 (1994).

6 Crystal data for hydrochloride of **4a** (R=Ph, R'=Me): $C_{23}H_{26}ClNO$, M=367.90, monoclinic, space group $P2_1$, a=14.221(3) Å, b=7.017(2) Å, c=10.591(3) Å, β=99.12(2)°, V=1043.4(4) Å^3, Z=2, Dc=1.17 gcm^{-3}, R=0.066, reflections used=1786.

7 For a recent review on selective reactions using allylic metals, see: Y. Yamamoto and A. Naoki, *Chem. Rev.*, **93**, 2207 (1993).