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Diastereofacial Discrimination in the Reaction of Chiral Alkoxymethyl Oxime Ethers with Allyl Metallic Reagents

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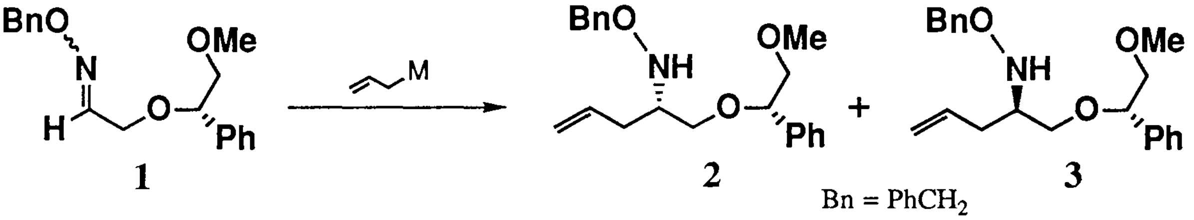
Allyl Grignard reagent complexed with cerium trichloride added to chiral (*E*)-alkoxymethyl oxime ether, derived from (*S*)-2-methoxy-1-phenylethanol, to give the corresponding (*S*)-amine stereoselectively, while the imino addition of allyllithium occurred with a preference for the opposite (*R*)-isomer. The configuration of the starting oxime ethers was found to greatly influence the diastereofacial discrimination.

The addition of organometallics to the imino functions, such as imine, hydrazone, oxime, and nitrone, constitutes a useful method for the preparation of amines, which are the key intermediates for the synthesis of nitrogen-containing biologically active substances, such as amino acid, β-lactam, and alkaloid. A particularly attractive feature of this method is the potential for asymmetric synthesis using chiral imine derivatives. Recently, the subject for the high stereocontrol has been addressed by chiral modification of the substrates which produce one of two isomers,1) however, obtaining both enantiomers of amines from a same starting material is still strongly required because the availability of chiral auxiliaries has frequently limited the preparation of amines to one optical isomer only. We previously reported that diastereofacial discrimination by judicious choice of organometallics could be achieved in the addition reaction to the chiral ketones possessing two heteroatoms in neighborhood of carbonyl group to give either isomer, respectively.2) Those results prompted us to develop the diastereofacial differentiating reaction in the addition of organometallics to carbon-nitrogen double bond. Among the imino function derivatives, oxime and oxime ether are the attractive compounds because of easy handling by their stability and easy separation of (*E*)- and (*Z*)-isomers, which makes it possible to investigate the effect of the lone electron-pair of imino nitrogen to the stereochemical course. Now we wish to report that either diastereofacial differentiating reaction of allyl metallic reagents to chiral alkoxymethyl oxime ether to afford either isomer depending on the metal used, respectively.

First, the reaction of a mixture of (*Z*)-α-((*S*)-2-methoxy-1-phenylethoxy)acetaldehyde *O*-benzyloxime (**1Z**) and the corresponding (*E*)-isomer **1*E***3) with 1.1 molar amounts of allyl Grignard reagent in THF at -100 - -78 °C was examined. After the the reaction mixture was hydrolyzed with sat. aq NH_4Cl followed by extraction



Bn = $PhCH_2$

Table 1. Reaction of chiral oxime ether **1** with allyl metallic reagents

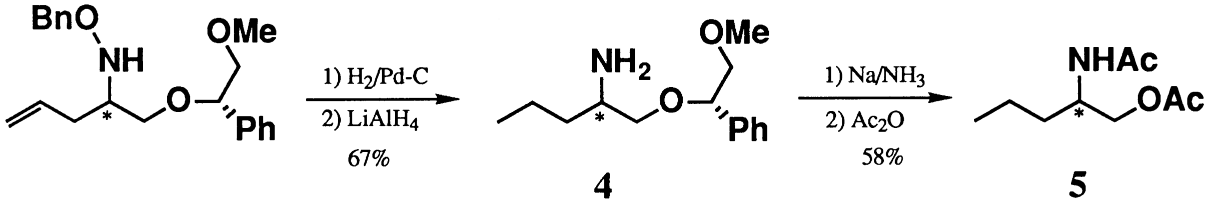
Entry	**1**	M[a)]	Solvent	Temp/ °C	Yield/%	**2** : **3**[b)]
1	*Z* and *E*[c)]	MgBr[d)]	THF	-100 – -78	59	47 : 53
2		MgBr[d)] - $CeCl_3$	THF	-78 – rt	45	82 : 18
3		Li[d)]	THF	-100	58	16 : 84
4	*Z*	MgBr[d)]	THF	-78	77	40 : 60
5		MgBr[d)] - $CeCl_3$	THF	-78 – rt	42	54 : 46
6		Li[d)]	THF	-100 – -78	86	32 : 68
7	*E*	MgBr[d)]	THF	-78	81	42 : 58
8		MgBr[d)] - $CeCl_3$	THF	-78 – rt	22	79 : 21
9		MgBr[e)] - $CeCl_3$	THF	-78 – -50	87	86 : 14
10		Li[d)]	THF	-100	99	3 : 97
11		Li[d)]	Et_2O	-100	71	8 : 92
12		Li[d)] - $CeCl_3$	THF	-78 – rt	47	8 : 92

a) The molar ratio of allyl metallics to oxime ether was 1.1 (Entries 1 - 3) or 2.0 - 3.0 (Entries 4 - 12). b) The ratios were determined by HPLC (Finepak SIL, hexane : 2-propanol = 200 : 1). c) A 44 : 56 mixture of **1*Z*** and **1*E*** was used. d) Allyl metallic reagent prepared in Et_2O was used. e) Allyl Grignard reagent prepared in THF was used.

and purification by TLC on silica gel, (*S*)-*N*-benzyloxy-1-((*S*)-2-methoxy-1-phenylethoxy)-4-penten-2-ylamine (**2**) and the corresponding (*R*)-amine **3** were obtained in a total yield of 59%, and 29% of unreacted oxime ether, whose configuration was predominantly Z, was recovered. As shown in the Table 1, the ratio of the obtained amines was determined to be **2** : **3** = 47 : 53 by HPLC analysis (Entry 1). When the oxime ethers were treated with allyl metallic reagent, prepared from allylmagnesium bromide and cerium trichloride previously,[4)] at -78 °C - rt, the stereoselectivity was improved to be 82 : 18 (Entry 2). In this reaction, 45% of the starting oxime ether **1** was recovered, whose configuration was also predominantly Z. On the other hand, the reaction of allyllithium at -100 °C furnished the opposite (*R*)-isomer **3** (Entry 3) and *ca.* 1 : 1 mixture of **1*Z*** and **1*E*** was recovered in 23% yield.

These results, especially in the case of allylmagnesium bromide-cerium trichloride, suggested that the stereoselectivity and the reactivity were affected by the configuration of chiral oxime ethers. Then, after the separation of (Z)- and (*E*)-oxime ethers, the nucleophilic addition was precisely investigated. The reaction of chiral (*Z*)-oxime ether **1*Z*** with allyl Grignard reagent, allyl Grignard reagent-cerium trichloride, and allyllithium showed only poor facial discrimination (Entries 4 - 6). In the addition reaction to (*E*)-oxime ether **1*E*** instead of (Z)-oxime ether **1Z**, although allylmagnesium bromide gave low selectivity (Entry 7), the combined use of cerium trichloride with Grignard reagent enhanced *si*-facial attack to mainly afford the corresponding (*S*)-amine **2** (Entry 8). When allylmagnesium bromide prepared in THF was used with cerium trichloride, the selectivity became higher than that using Grignard reagent prepared in Et_2O (Entry 9). In contrast, compared with the case of allylmagnesium bromide-cerium trichloride, virtual reversal of stereoisomer preference was accomplished utilizing allyllithium, *i.e.*, the treatment of (*E*)-oxime ether **1*E*** with allyllithium at -100 °C afforded (*R*)-product **3** with high stereoselectivity by the attack from *re*-face (Entry 10). In the case of allyllithium, THF as a solvent realized more efficient stereoselection than Et_2O (Entry 11). To our surprise, the addition reaction to **1*E*** by allyllithium complexed with cerium trichloride5) also furnished (*R*)-product **3** stereoselectively (Entry 12).

The stereochemistry at chiral center newly formed was determined as follows: Hydrogenation of carbon-carbon double bond in the obtained *N*-benzyloxyamine and the cleavage of nitrogen-oxygen bond by $LiAlH_4$ afforded amine **4**. Then, the former amine **4** was further transformed into **5** by the removal of chiral auxiliary by the Birch reduction and acetylation of the resulting amino alcohol. The specific rotation of the diacetate **5**, to which a 24 : 76 mixture of **2** and **3** was converted, was $[\alpha]_D^{23}$ +23.1° (c 0.99, MeOH). On the other hand, the $LiAlH_4$ reduction of (*S*)-norvaline followed by acetylation gave (*S*)-**5** ($[\alpha]_D^{23}$ -39.7° (c 0.86, MeOH)). By the comparison of the measured specific rotation, the stereochemistry at C_2 in **2** was concluded to be *S* and in **3** to be *R*, respectively.



Although the actual stereochemical course is still an open question, it was presumed that the simultaneous coordination to metal by the three heteroatoms, was crucial for either diastereofacial discrimination. That is, in the case of (*Z*)-oxime ether **1*Z***, the simultaneous chelation of two ethereal oxygens to the metal, which activates carbon-nitrogen double bond, is impossible (Fig. 1). One the other hand, nitrogen of oxime ether and two ethereal oxygens in (*E*)-oxime ether **1*E*** can simultaneously coordinate the metal to generate fused double five-membered chelate structure (Fig. 2). Therefore, the formation of such fused chelate might be effective for the activation of imino function6) and the efficient diastereofacial discrimination, that enabled the formation of each diastereomer depending on the different coordination ability of metal used.2)

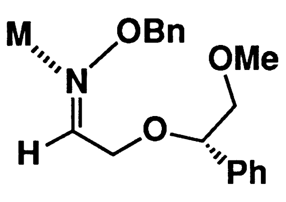


Fig. 1.

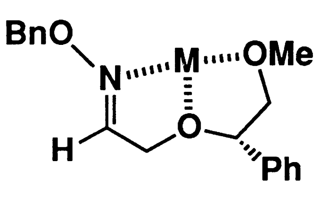


Fig. 2.

The obtained *N*-benzyloxyamine **2** or **3** is a useful chiral building block possessing carbon-carbon double bond and oxygen functional group. Further, (*Z*)- and (*E*)-oxime ethers could be separated and (*Z*)-oxime ether **1*Z*** was easily isomerized to the equilibrium mixture of (*E*)- and (*Z*)-oxime ethers by the treatment with a catalytic amount of $BnONH_2 \cdot HCl$.7) Thus this method provides a new entry for the preparation of both enantiomers of nitrogen containing compounds from a same starting material by the choice of the appropriate metal.10)

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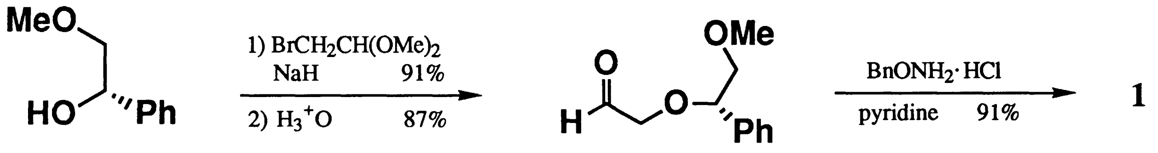
3) Chiral alkoxymethyl oxime ethers were easily synthesized from (*S*)-2-methoxy-1-phenylethanol8) in three steps as drawn below and the obtained (*Z*)- and (*E*)-isomers (**1Z** : **1*E***= 44 : 56) could be easily separated by silica gel chromatography (benzene - Et$_2$O). The configuration of oxime ethers was determined by the comparison of their ^{1}H NMR chemical shifts;9) **1Z** (CCl$_4$); δ 4.22 (BnON=CHC$\underline{\mathrm{H}}_2$-), 6.83 (BnON=C$\underline{\mathrm{H}}$CH$_2$-). **1*E*** (CCl$_4$); δ 3.98 (BnON=CHC$\underline{\mathrm{H}}_2$-), 7.41 (BnON=C$\underline{\mathrm{H}}$CH$_2$-).



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