

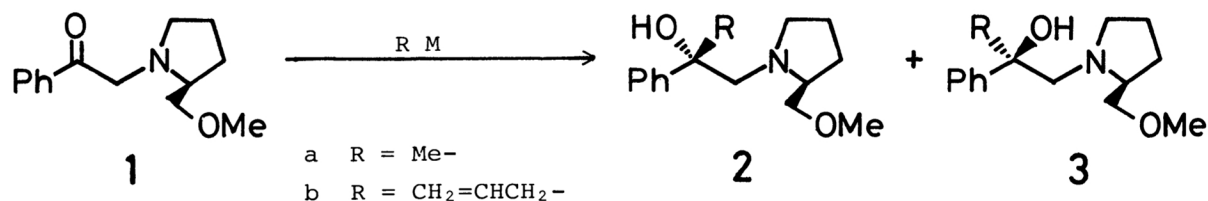
Diastereofacial Control in the Reaction of
Chiral α -Amino Ketones with Several Organometallics

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The addition reaction of organometallics to chiral α -amino ketones, prepared from α -halo ketones and (S)-2-methoxymethylpyrrolidine as a chiral auxiliary, gave different diastereomers of chiral amino alcohols depending on the difference of coordination ability of the metal used, *i.e.* organometallics such as Grignard reagent, organozinc, and cerium reagents preferred *re*-face attack, while organolithium compound attacked from *si*-face.

In view of the tremendous advance in the development of asymmetric synthesis, diastereoselective addition reaction of organometallics to chiral carbonyl compounds constitutes a new strategy for asymmetric carbon-carbon bond formation. A number of methods have been reported to synthesize one of two stereoisomers by the addition reaction utilizing a chiral auxiliary derived from naturally occurring chiral compounds.¹⁾ There still remains, however, the important problem to obtain different two diastereomers in high diastereomeric excess from the same starting materials, which is extremely useful in organic synthesis. In regard to obtaining different stereoisomers, several examples were published such as nucleophilic addition to chiral α -ketoacetals,^{2a)} allylation of chiral α -keto amides,^{2b)} and alkylation of chiral keto amins.^{2c)} Concerned with this problem,³⁾ we have already reported that the reaction of chiral cyclic α -ketoenamines, prepared from cyclic α -diketones and (S)-2-methoxymethylpyrrolidine,⁴⁾ with Grignard reagents and organolithium reagents gave the corresponding (R)- and (S)- α -hydroxy ketones with high enantiomeric excess after hydrolysis, respectively.⁵⁾ We wish to disclose here another example for highly diastereofacial controlled reaction of acyclic α -aminoketones with several organometallics, which furnished both stereoisomers of the corresponding α -amino alcohols.

The addition reaction of methyl Grignard reagent to α -((S)-2-methoxymethylpyrrolidino)acetophenone (1), prepared easily from α -bromoacetophenone and (S)-2-methoxymethylpyrrolidine,⁴⁾ in ether at -78°C gave (2S)-1-((S)-2-methoxymethylpyrrolidino)-2-phenyl-2-propanol (2a) ($[\alpha]_{\text{D}}^{23} -60.2^\circ$ (c 0.76, EtOH)) in 51% yield. The diastereomeric ratio of the addition products was determined to be 95% de by $^1\text{H-NMR}$ of C_2 -methyl signals. The absolute configuration of newly formed chiral center could be determined to be S by transforming to the corresponding epoxide (*vide infra*). In the case of allylmetals, Grignard reagent gave (2S)-allylated product with 2% de, however, allylzinc bromide gave the same product with high optical purity ($[\alpha]_{\text{D}}^{23} -16.7^\circ$ (c 0.34, EtOH)). On the other hand, when methyllithium

Table 1. Reaction of chiral α-aminoacetophenone 1 with organometallic reagents^{a)}

RM	Solvent	Yield of (2+3)/ %	%de	Config. ^{d)}
MeMgBr	THF	51	95 ^{b)}	S
MeLi	Et ₂ O	49	95 ^{b)}	R
ZnBr	THF	67	100 ^{c)}	S
Li	Et ₂ O	48	38 ^{c)}	R

a) The reaction was performed at -78 °C for 4.5-8.5 h. b) The diastereomeric excess was determined by integration of C₂-methyl protons in ¹H-NMR spectra. c) The ratios was measured by capillary GLPC (SE-30). d) Configuration of major diastereomer at C₂.

was used in place of the Grignard reagent, diastereoselection was dramatically changed to give α-amino alcohol 3a with R configuration in 95% de ($[\alpha]_D^{23}$ -9.52° (c 0.92, EtOH)). Analogously, allyllithium gave the corresponding amino alcohol 3b with R configuration in 38% de. These results are summarized in Table 1.

When methyl ketone was used instead of phenyl ketone, the analogous tendency was observed in the diastereoselection. α-((S)-2-Methoxymethylpyrrolidino)acetone (4), prepared from α-chloroacetone and (S)-2-methoxymethylpyrrolidine, reacted with phenyl Grignard reagent at -78 °C to give (2R)-1-((S)-2-methoxymethylpyrrolidino)-2-phenyl-2-propanol (5a = 3a) with 95% de ($[\alpha]_D^{23}$ -9.3° (c 0.54, EtOH)). The reaction with 4-phenylbutylmagnesium chloride gave (2R)-1-((S)-2-methoxymethylpyrrolidino)-2-methyl-6-phenyl-2-hexanol (5b) in 91% de. Addition of cerium(III) chloride to the Grignard reagent⁶⁾ increased the diastereoselectivity up to over 96% de of the same configuration ($[\alpha]_D^{23}$ -29.3° (c 0.75, EtOH)). In the case of allylmetals, Grignard reagent gave (2R)-allylated product with 18% de, however, allylzinc bromide gave the same product with high optical purity ($[\alpha]_D^{23}$ -48.9° (c 0.60, EtOH)). On the other hand, no diastereoselection was observed in the reaction with phenyllithium, while the corresponding (2S)-α-amino alcohol 6a was obtained in 13% de when the lithium reagent was used together with lithium bromide in order to enforce the coordination ability with the hetero atoms. Addition reaction of 4-phenylbutyl- and allyllithium gave the corresponding (S)-amino alcohols 6, albeit with low selectivity. These results are summarized in Table 2.

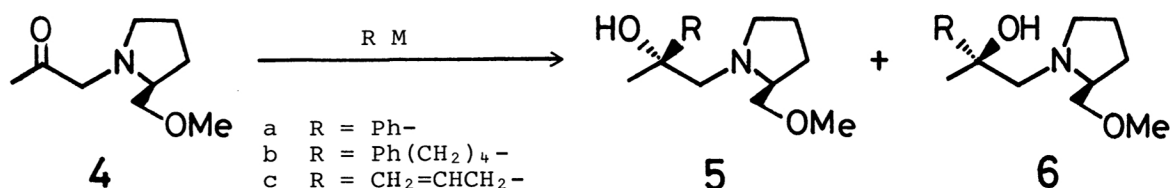
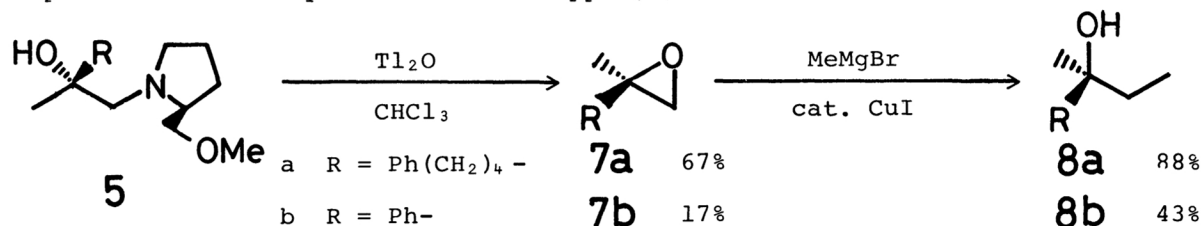


Table 2. Reaction of chiral α -aminoacetone 4 with organometallic reagent^{a)}

RM	Solvent	Yield of (5+6)/ %	% de ^{b)}	Config. ^{c)}
PhMgCl	Et ₂ O	64	95	R
Ph-  MgCl + CeCl ₃	THF	83	>96	R
Ph-  Li	THF	65	18	S
 ZnBr	THF	78	100	R
 Li	Et ₂ O	49	25	S

a) Addition reaction was performed at -78 °C for 3-10.5 h. b) Determined by the measurement of C₂-methyl protons in ¹H-NMR spectra. c) Configuration of major diastereomer at C₂.

The obtained chiral α -amino alcohol 5a was able to be converted to the corresponding chiral oxirane 7a through deamination by the treatment with thallium(I) oxide in chloroform⁷⁾ without racemization.⁸⁾ The absolute configuration of tertiary carbon attached to the hydroxyl group in the chiral amino alcohol 5a was determined to be R by conversion into (S)-(-)-3-methyl-7-phenyl-3-heptanol,^{9a)} which was furnished by the reaction of the oxirane 7a with methyl Grignard reagent in the presence of catalytic amount of copper(I) iodide. Amino alcohol 5b was also



converted to (S)-(-)-2-phenyl-2-butanol (8b).^{9b)} These results show that the organometallics such as Grignard reagents, organozinc and cerium compounds with stronger coordination ability and larger coordination number than lithium compounds preferred the *re*-face attack with over 91% de. It is noteworthy that allylzinc derivative gave the optically pure amino alcohol. Surprisingly, the diastereofacial differentiation by those organometallics was opposite to the case of chiral α -ketoenamines previously reported,⁵⁾ that is, the direction of attack of Grignard reagents preferred from *si*-face of α -ketoenamines and *re*-face of α -amino ketones (1 or 4), and the attack of organolithium reagents was reversal.¹⁰⁾

Although the actual stereochemical course is not ascertained, the present diastereofacial control may be explained as follows. Since Grignard reagent is known to shape octahedral six-membered adducts,¹¹⁾ it might form the rigid structure 9 with chiral α -amino ketone. Namely, the three hetero atoms of α -amino ketone and bromine located on the same plane, and the attack of the alkyl group onto the carbonyl carbon occurred from *re*-face because C₂-methylene group of pyrrolidine

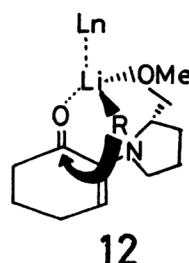
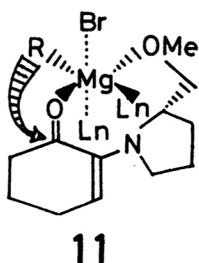


disturbs its approach from *si*-face. The reaction of organozinc compounds seems to proceed in the similar way. On the other hand, the alkyl group of organolithium compound, which is found to be mostly four-fold tetrahedral coordination,¹¹⁾ transfers to the carbonyl carbon from the less-hindered *si*-face as illustrated in 10.

As described above, the present method utilizing different coordination states of organometallics provides a useful way for the selective syntheses of different diastereomers starting from chiral carbonyl compounds with the same chiral auxiliary.¹²⁾

References

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- 10) The coordination states shown in the previous paper⁵⁾ should be revised as 11 and 12, in which nitrogen atom of enamine does not take part in the coordination. The authors are grateful to Professor Dieter Seebach for suggestion to the coordination states.



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