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

Tamotsu FUJISAWA,* Makoto FUNABORA, Yutaka UKAJI, and Toshio SATO
Chemistry Department of Resources, Mie University, Tsu, Mie 514

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 aminals.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**) ($[\alpha]_D^{23}$ -60.2°(c 0.76, EtOH)) in 51% yield. The diastereomeric ratio of the addition products was determined to be 95% de by ^{1}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 ($[\alpha]_D^{23}$ -16.7°(c 0.34, EtOH)). On the other hand, when methyllithium

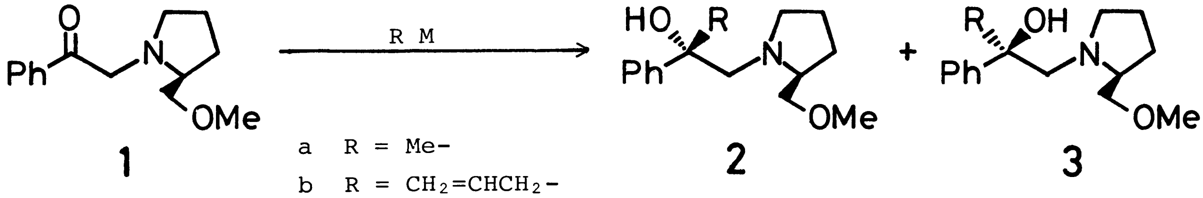
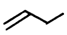
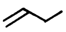


Table 1. Reaction of chiral α-aminoacetophenone **1** with organometallic reagents[a)]

RM	Solvent	Yield of (2+3)/ %	%de	Config.[d)]
MeMgBr	THF	51	95[b)]	S
MeLi	Et_2O	49	95[b)]	R
 ZnBr	THF	67	100[c)]	S
 Li	Et_2O	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 C_2-methyl protons in ^{1}H-NMR spectra. c) The ratios was measured by capillary GLPC (SE-30). d) Configuration of major diastereomer at C_2.

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-methoxymethyl-pyrrolidino)-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-methoxy-methylpyrrolidino)-2-methyl-6-phenyl-2-hexanol (**5b**) in 91% de. Addition of cerium(III) chloride to the Grignard reagent[6)] 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 obtaind 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.

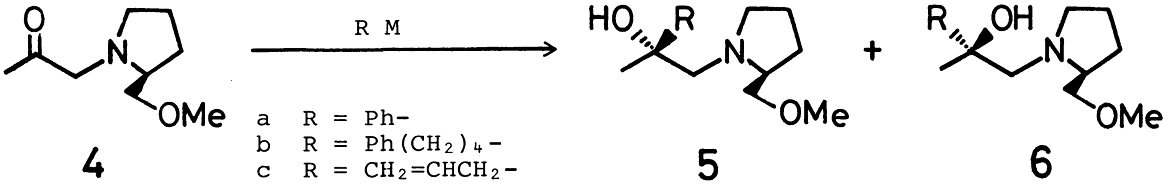
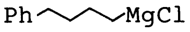
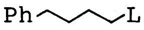
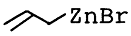
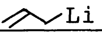
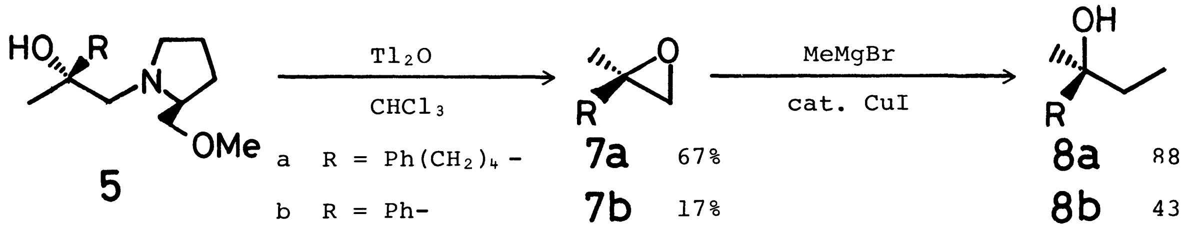


Table 2. Reaction of chiral α-aminoacetone **4** with organometallic reagent[a)]

RM	Solvent	Yield of (5+6)/ %	% de[b)]	Config.[c)]
PhMgCl	Et_2O	64	95	R
 + $CeCl_3$	THF	83	>96	R
	THF	65	18	S
	THF	78	100	R
	Et_2O	49	25	S

a) Addition reaction was performed at -78 °C for 3-10.5 h. b) Determined by the measurement of C_2-methyl protons in ^{1}H-NMR spectra. c) Configuration of major diastereomer at C_2.

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 chloroform[7)] 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 diastereoface 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)]



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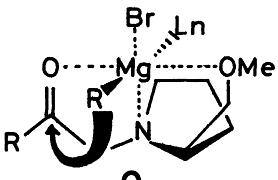
a R = $Ph(CH_2)_4$- **7a** 67% **8a** 88%

b R = Ph- **7b** 17% **8b** 43%

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 C_2-methylene group of pyrrolidine



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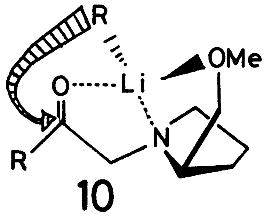

10

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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3) Other examples for stereoselective preparation of two diastereomers by the reaction of organometallics with ketones; see P. A. Wade, D. T. Price, J. P. McCauley, and P. J. Carroll, J. Org. Chem., 50, 2804 (1985) and references cited therein.
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8) No racemization was observed by the measurement of ^{1}H-NMR utilizing $Eu(hfc)_3$.
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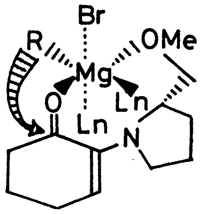
10) The coordination states shown in the previous paper5) should be revised as **11** and **12**, in which nitrogen atom of enamine does not take part in the coordination. The authors are grateful to Professor Dieter Seebach for suggestion to the coordination states.



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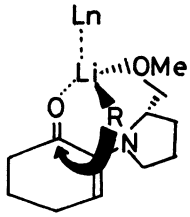

12

11) D. Seebach, J. Hansen, P. Seiler, and J. M. Gromek, J. Organomet. Chem., 285, 1 (1985) and references cited therein.
12) The present work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture.

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