CHEMISTRY LETTERS, pp. 2055 - 2058, 1984.

DIASTEREOFACE-DIFFERENTIATING ADDITION OF ORGANOMETALLICS TOWARD CHIRAL α-KETOENAMINES

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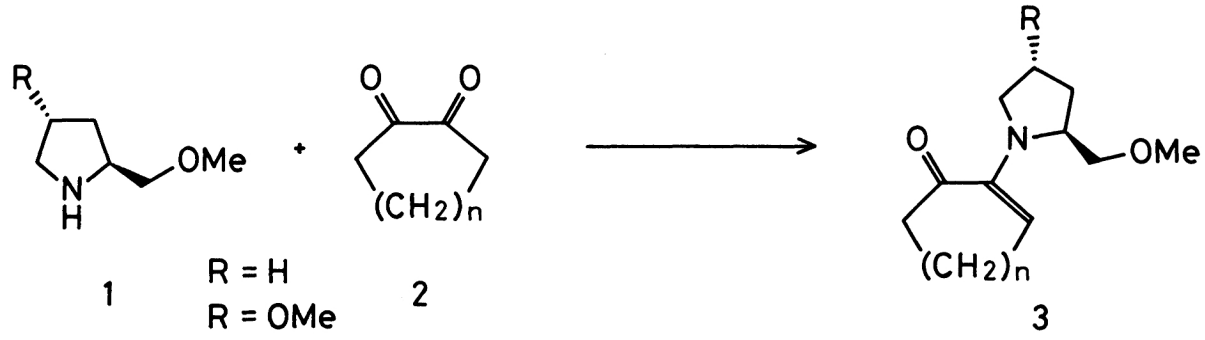
The diastereoface-differentiating reaction of Grignard reagents or organolithium reagents toward chiral cyclic α-keto-enamines, prepared from the corresponding cycloalkane-1,2-dione and optically active pyrrolidine derivatives, was found to give, after hydrolysis, (*R*)- or (*S*)-α-hydroxycycloalkanones, respectively, in high enantiomeric excess.

In the recent development of asymmetric synthesis, the advantage of use of symmetrical compounds has been demonstrated.[1] A number of methods have been reported to synthesize optically active molecules from symmetrical ones. For example, a regioselective substitution of 3-methylglutaramide,[2] a selective reduction of carbonyl group of chiral imide,[3] an asymmetric acylation of meso-1,2-diols,[4] construction of steroid CD skeleton by the high enantioselective cyclization of prochiral compounds,[5,6] catalytic asymmetric hydrogenation of cyclic anhydrides using ruthenium(II) chiral phosphine complex[7] and α-alkylation of chiral enamine or imine[8-11] were representative. Thus, among various types of asymmetric synthesis, it is one of the effective method to synthesize optically active compounds by enantioselective conversion of one of two prochiral groups in the symmetrical molecule. We wish to describe here that both enantiomers of α-substituted-α-hydroxy ketones with high optical purity were obtained by diastereoface-differentiating addition of organometalic reagents to optically active α-ketoenamines, which were synthesized from symmetrical cyclic 1,2-diketones and chiral pyrolidines derived from (*S*)-proline or (2*S*,4*R*)-hydroxyproline. Although the electrophilic asymmetric α-alkylation of chiral cyclic or acyclic enamine has been reported,[8-11] our nucleophilic asymmetric α-alkylation of chiral cyclic α-ketoenamine is an unprecedented enantioselective synthesis.



1 2 3

Table 1. Preparation of Chiral α-Ketoenamine (3)

Compound	Pyrrolidine R	1,2-Diketone n	Temp	Yield/%[a]	$[\alpha]_D^{22}$ (C_6H_6)
a	H	1	rt[b]	85	-193.0°
b	H	2	rt	88	-144.4°
c	OMe	2	rt	85	-189.2°
d	H	3	rt	72	-8.02°
e	OMe	3	rt	75	-13.9°
f	H	4	benzene reflux	58	+75.4°

a) All products gave satisfactory NMR and IR spectra. b) rt = room temperature.

These 1,2-cycloalkanedione enamines were prepared as follows: (*S*)-2-methoxymethylpyrrolidine 1 (R = H) or (2*S*,4*R*)-2-methoxymethyl-4-methoxypyrrolidine 1 (R = OMe) and 1,2-cycloalkanedione 2 was stirred in benzene in the presence of 3Å molecular sieves at room temperature or under reflux. After 10 hours, molecular sieves were removed and then 1,2-cycloalkanedione enamine 3 was isolated by distillation. These results are summarized in Table 1.

Initial examination by using methylmagnesium bromide and the α-ketoenamines 3 gave α-hydroxy-α-methylcycloalkanones 4 in reasonable chemical yields and high optical yields after hydrolysis. These results were summarized in Table 2. The high enantioselectivity was obtained particularly in the case of α-ketoenamines with 5-7 membered ring. 1,4-Adducts could not be detected in all cases. The methoxy group at 4 position on pyrrolidine ring did not influence the asymmetric induction. Addition reactions of some kinds of Grignard reagents to the α-ketoenamine 3b were achieved. Methyl, ethyl and vinyl Grignard reagents gave the corresponding 2-substituted-2-hydroxycyclohexanone 4 with high optical purity. But in the case of phenyl Grignard reagent, the optical yield was decreased (entry 9). This may be due to weaker coordination of the magnesium with heteroatoms of α-ketoenamine than that of other Grignard reagents with heteroatoms.

On the other hand, in the addition reaction of some kinds of organolithium

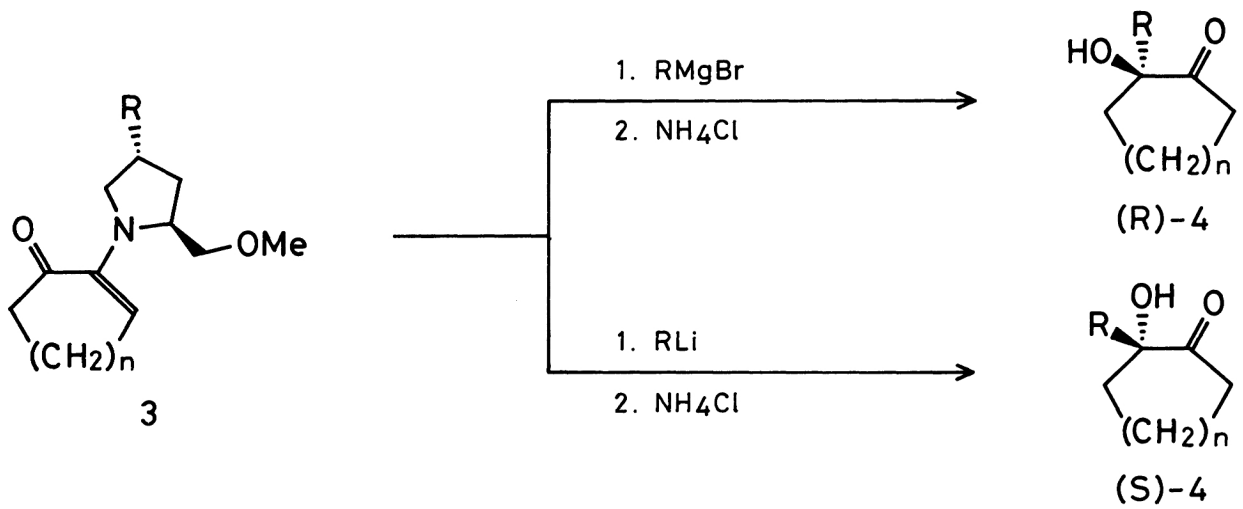


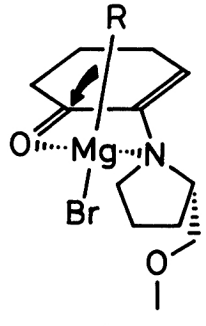
Table 2. Preparation of α-Hydroxy-α-substituted Cycloalkanone

Entry	Enamine	RM	Yield/%	$[\alpha]_D^{22}$ ($CHCl_3$)	ee/%[a]	Configuration[11]
1	a	MeMgBr	55	+27.4°	95[b]	*R*
2	b	MeMgBr	67	+100.5°	95[b]	*R*
3	c	MeMgBr	65	+99.8°	95[b]	*R*
4	d	MeMgBr	55	+69.0°	95[c]	*R*
5	e	MeMgBr	57	+70.1°	95[c]	*R*
6	f	MeMgBr	50	+38.1°	80[c]	*R*
7	b	EtMgBr	70	+131.5°	92[b]	*R*
8	b	⩔MgBr	57	+145.2°	95[b]	*S*
9	b	PhMgBr	50	+169.3°	58[d]	*S*
10	b	MeLi	76	-105.3°	98[e]	*S*
11	b	EtLi	47	-92.9°	65[e]	*S*
12	b	⩔Li	88	-102.8°	70[e]	*R*
13	b	PhLi	44	-67.8°	23[d]	*R*

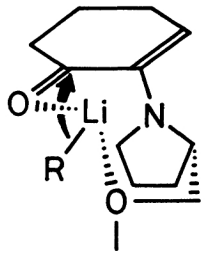
a) The optical yield was determined as follows. b) After the two diastereomeric diol obtained by the reduction of α-hydroxycycloalkanone with lithium aluminum hydride was separated by SiO_2-TLC, each diol was converted into the corresponding MTPA ester, whose optical purity was determined by NMR analysis using $Eu(fod)_3$. c) The optical purity was determined by NMR analysis using $Eu(hfc)_3$. d) The reduction of α-hydroxycyclohexanone with zinc borohydride gave *erythro* 1-phenylcyclohexane-1,2-diol ($[\alpha]_D^{22}$ -31.3° (c 0.659, C_6H_6)) which was calculated as 58% ee in comparison with the reported value.[12] e) Compared with the adduct using Grignard reagent.

reagents to the same α-ketoenamine 3b, the reaction of methyllithium gave also the adduct with high optical yield as the case of Grignard reagent. To our surprise, the absolute configuration of 2-methyl-2-hydroxycyclohexanone thus obtained is opposite of *R*. In the cases of ethyl, vinyl and phenyllithium compounds, adducts with opposite specific rotations were obtained, but these optical yields were lower than that of the adducts using the corresponding Grignard reagent.

This enantioselectivity may be reasonably explained by the following coordination states. The methoxymethyl group on the pyrrolidine ring is fixed in the reverse side of carbonyl group by the electrostatic repulsion between the



A



B

carbonyl oxygen atom and the methoxy oxygen atom, and is directed to α face opposite to the lone pair electron of the nitrogen atom which overlaps with the orbital of π-electron of the doulbe bond. The magnesium metal in the Grignard reagents can coordinate with two kinds of heteroatoms, nitrogen and carbonyl oxygen atoms[13] from the opposite side of the methoxymethyl group. Therefore substituent of Grignard reagents attacks the carbonyl carbon from β face as shown in A. On the other hand, in the case of organolithium reagents, the metal is known to coordinate strongly with both the carbonyl oxygen and methoxy oxygen atoms.[14] Accordingly substituent group of lithium reagent can attack the carbonyl carbon from α face as shown in B.

Typical experimental procedure is described for the preparation of (*R*)-2-hydroxy-2-methylcyclohexanone: A solution of 2-((*S*)-2-methoxymethylpyrrolidino)-2-cyclohexen-1-one in ether was cooled to -78 °C, and a solution of 2.5 equivalent of methylmagnesium bromide in ether was added. After being stirred for 2 h at the same temperature, the reaction was quenched by adding saturated ammonium chloride solution. Extraction with ether, drying over anhydrous sodium sulfate, and evaporation of the solvent under reduced pressure, afforded the crude product, which was purified by silica-gel TLC to give (*R*)-2-hydroxy-2-methylcyclohexanone in 67% yield. 95% ee $[\alpha]_D^{22}$ +100.5° (c 0.962, $CHCl_3$).

As shown above, because of different coordination between chiral α-ketoenamine and Grignard reagent or lithium reagent, the diastereoface-differentiating reaction of organometalics to chiral α-ketoenamine could be achieved.

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(Received September 3, 1984)