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VERSATILE METHOD FOR THE PREPARATION OF OPTICALLY ACTIVE α-HYDROXY ALDEHYDES WITH DESIRED CONFIGURATIONS

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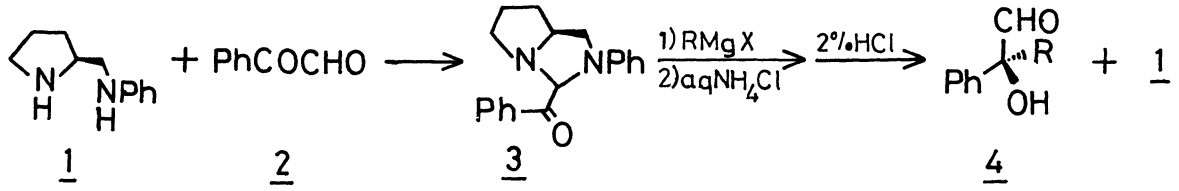
A convenient method was established for the asymmetric synthesis of various α-hydroxy aldehydes with high optical yields starting from methoxycarbonyl aminal, prepared from methyl hydroxymethoxyacetate and (S)-2-(anilinomethyl)pyrrolidine. The configurations of α-hydroxy aldehydes are arbitrarily controlled by the order of the introduction of two substituents in the α-hydroxy aldehydes originated from Grignard reagents.

We recently reported an asymmetric synthesis of α-hydroxy aldehydes with high optical yields starting from 2-benzoyl-3-phenyl-1,3-diazabicyclo[3.3.0]octane 3, prepared from phenylglyoxal and (S)-2-(anilinomethyl)pyrrolidine.[1] But, in the synthesis, one of the substituents in the resulting α-hydroxy aldehydes was limited to phenyl group as the aldehydes were derived from phenylglyoxal.



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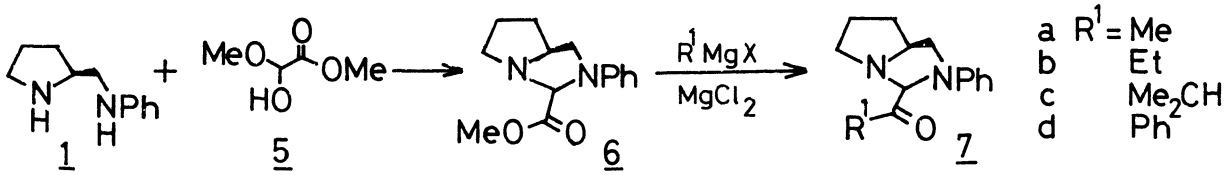
In order to synthesize various α-hydroxy aldehydes, we have investigated a new route to keto aminals 7 with arbitrary substituents. A preparation of methyl substituted keto aminal 7a was studied first. An attempt to prepare keto aminal 7a directly from diamine 1 and methylglyoxal was unsuccessful. Then we have chosen methoxycarbonyl aminal 6 as a precursor and various keto aminals were successfully prepared by the Grignard reaction.

Methoxycarbonyl aminal 6 was prepared from diamine 1 and methyl hydroxymethoxyacetate. Treatment of methoxycarbonyl aminal 6 with Grignard reagents in the presence of magnesium chloride[2] afforded various keto aminals[3] in good yields as shown in Table 1.

Typical experimental procedure is described for the preparation of keto aminal 7a; methyl hydroxymethoxyacetate (15.8 mmol) was treated with diamine 1 (15.0 mmol) with removal of water azeotropically in refluxing benzene for 30 min. The solvent was evaporated under reduced pressure and the resulting methoxycarbonyl aminal 6[4] was used without further purification. To a solution of 6 in THF was added anhydrous magnesium chloride and refluxed for 10 min. The solution was cooled to -70°C, and 1.36 equivalent of methyl magnesium bromide in ether was added. After one hour, saturated ammonium chloride solution was added to the reaction mixture. The mixture was extracted with ether and the ethereal extract was washed with saturated sodium chloride solution. The crude product was purified by alumina column chromatography and keto aminal 7a was isolated in 72% yield.



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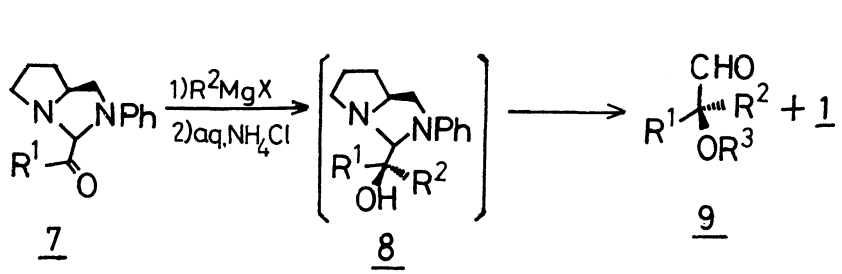
α-Hydroxy aldehydes were prepared in high optical yields by the further Grignard reaction of keto aminals and hydrolysis of the resulting hydroxy aminals 8. The results are summarized in Table 2 and typical experimental procedure is described for the preparation of α-hydroxy-α-phenyl propionaldehyde; to an ethereal solution of keto aminal 7a (1.1 mmol) was added phenyl magnesium bromide (2.2 mmol) in ether at -70°C. After an hour, saturated ammonium chloride solution was added to the reaction mixture. The ethereal layer was separated and washed with 1N sodium hydroxide solution. The ethereal layer was treated with 2% hydrochloric acid at 0°C for 12 hours. The ethereal layer was separated and washed with saturated sodium chloride solution. The solvent was evaporated under reduced pressure to yield oily substance. The crude product was purified by silica gel column chromatography and α-hydroxy-α-phenyl-propionaldehyde was isolated in 76% yield, which was thoroughly purified by short path distillation ($[\alpha]_D^{29}$ -255° (c 1.060, benzene)).



7 8 9

	R^1	R^2	R^3
a	Me	Ph	H
b	Me	Et	CH_2Ph
c	Me	CH_2=CH-	CH_2Ph
d	Et	Ph	H
e	Et	Me	CH_2Ph
f	Me_2CH-	Ph	H

Table 1. Preparation of keto aminals

	R^1MgX	Yield(%)[a]
a	MeMgBr	72
b	EtMgBr	28
c	$Me_2CHMgBr$	79
d	PhMgBr	77

a) Yields are based on diamine 1.

Table 2. Preparation of α-hydroxy aldehydes

	R^1	R^2MgX	Yield(%)	$[\alpha]_D$(c,C_6H_6)	ee(%)	config.
a	Me	PhMgBr	76	-255°(1.060)	99[e]	R
b	Me	EtMgBr	43[b,c]	+39°(1.027)[d]	78[f]	R
c	Me	CH_2=CHMgBr[a]	44[b]	+156°(0.963)[d]	93[g]	R
d	Et	PhMgBr	80	-256°(1.147)	100[h]	R
e	Et	MeMgI	41[b]	-39°(1.002)[d]	78[i]	S
f	Me_2CH-	PhMgBr	75	-308°(1.340)	>94[j]	R

a) The reaction temperature was raised gradually to 0°C after 20 hours.

b) Isolated as benzyl ether. The hydroxy aminal 8b,c,e was treated with NaH/$PhCH_2Br$ and hydrolyzed after purification by alumina column chromatography.

c) The intermediate aminal 8 was isolated in 92% yield.

d) $[\alpha]_D$ of the benzyl ether.

e) Based on $[\alpha]_D$+244° (c 1.138, benzene) as 95% ee reported in our previous paper.[1]

f) The optical yield was determined as follows. The benzyloxy aldehyde 9b was reduced with sodium borohydride to 2-benzyloxy-2-methylbutanol ($[\alpha]_D^{16}$-1.1° (c 1.050, MeOH)) and its hydrogenolysis with 5% Pd-C afforded 2-methyl-1,2-butanediol ($[\alpha]_D^{24}$+7.65°(neat)), whose enantiomeric excess was 78%, based on $[\alpha]_D^{22}$-4.8°(neat) as 49% ee reported in reference 5).

g) The optical yield was determined as follows. The benzyloxy aldehyde 9c was reduced with sodium borohydride to 2-benzyloxy-2-methyl-3-butenol ($[\alpha]_D^{16}$+10.6° (c 0.995, MeOH)). The alcohol was treatd with 5% Pd-C under hydrogen to yield 2-methyl-1,2-butanediol ($[\alpha]_D^{24}$+9.07(neat)), whose enantiomeric excess was 93% based on $[\alpha]_D^{22}$-4.8° as 49% ee reported in reference 5).

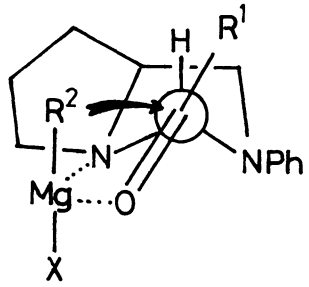
h) Based on $[\alpha]_D$+239° (c 1.048, benzene) as 94% ee reported in our previous paper.[1]

i) Based on $[\alpha]_D$+39° (c 1.027, benzene) as 78% ee described in f).

j) Based on $[\alpha]_D$+310° (c 1.031, benzene) as >95% ee reported in our previous paper.[1]

Since, according to the present method, the introduction of two substituents in α-hydroxy aldehydes is accomplished by the successive two Grignard reactions, it became possible to obtain desired configurations in the α-hydroxy aldehydes by choosing the order of the addition of the Grignard reagents. Namely, when R^1, introduced into the keto aminal 7 by the first Grignard reaction, has higher priority than R^2, introduced by the second Grignard reaction, the resulting α-hydroxy aldehyde has S configuration. On the other hand, when R^1 has lower priority than R^2, the configuration of the α-hydroxy aldehyde becomes R.

The configurations of the α-hydroxy aldehydes obtained by the present experiments support our assumption, that is, magnesium of the Grignard reagent complexes with the carbonyl oxygen and the nitrogen on the pyrrolidine ring of the keto aminal, which can more strongly complex than the more electron deficient nitrogen substituted by phenyl group. This leads to a rigid magnesium complex, then the substituent originated from the Grignard reagent migrates to the carbonyl carbon from the less hindered side as illustrated in figure.



References and Notes

1) T.Mukaiyama, Y.Sakito, and M.Asami, Chem. Lett.,1978, 1253.
2) When magnesium chloride was not used, the yields became lower.
3) All keto aminals are fully characterized by IR and NMR data.
4) The methoxycarbonyl aminal 6 could be purified by alumina column chromatography or short path distillation. NMR(CCl_4) δ = 1.5-2.3 (4H, m), 2.3-4.1 (5H, m), 3.5 (3H, s), 4.6 (1H, s), 6.2-7.1 (5H, m). Found: C, 68.26; H, 7.64; N, 11.65%. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37%.
5) W.Kirmse, H.Arold, and B.Kornrumpf, Chem. Ber., 104, 1783 (1971).

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