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ENANTIOSELECTIVE REDUCTION OF KETONES WITH OPTICALLY ACTIVE 2,2'-DIAMINO-6,6'-DIMETHYLBIPHENYL-LITHIUM ALUMINUM HYDRIDE COMPLEX

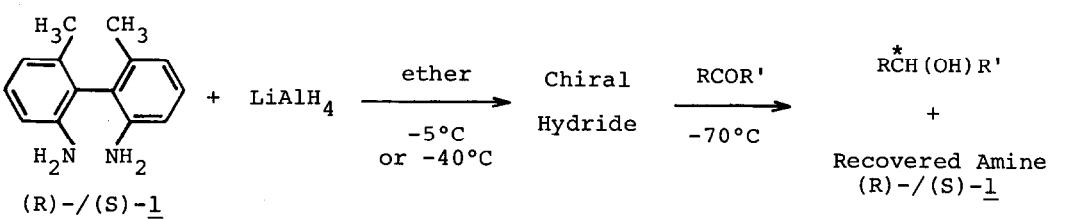
Hiroshi Suda*, Masatoahi Motoi, Masatoshi Fujii,
Shigeyoshi Kanoh and Hiroshi Yoshida

Department of Industrial Chemistry, Faculty of Technology,
Kanazawa University, Kodatsuno, Kanazawa 920, Japan

Summary : Enantioselective reductions of prochiral ketones with chiral hydride reagent prepared from optically active 2,2'-diamino-6,6'-dimethylbiphenyl and lithium aluminum hydride were accomplished in O.Y. more than 50%.

Recently a number of enantioselective reductions of prochiral carbonyl compounds with chiral hydride reagents have been performed successfully. However, most of them have used natural or artificial optically active substances,[1,2] such as sugar, alkaloid, alcohol, amine and aminoalcohol, of which chiralities are drived from asymmetric carbon(s) or other atom(s).

Having been interested in some biphenyl derivatives are dissymmetric and are stable against racemization,[3] we have studied several uses of chiral biphenyl derivatives for enantioselective synthesis. Here we wish to describe an asymmetric reduction of prochiral ketone with a complex hydride reagent containing optically pure 2,2'-diamino-6,6'-dimethylbiphenyl (1) as a chiral ligand. Recently, Noyori *et al.*[4] reported that phenyl alkyl ketones were selectively reduced in excellent optical yield(O.Y.) with a hydride complex from optically pure 2,2'-dihydroxy-1,1'-binaphthl as a ligand. This is similar to ours in the use of a dissymmetric ligand.



The amine 1 was prepared from o-toluidine through several steps by a method described in the literatures[5] in about 33% overall yield. The racemic product was resolved by use of D/L-tartaric acid in ethanol. (R)-1: mp 159-160°C, $[\alpha]_D^{33}$ -37.3°(c 1.05,N-HCl), $[\alpha]_D^{33}$ +52.4°(c 1.00,EtOH); (S)-1: mp 159-

160°C, $[\alpha]_D^{33}$ +37°(c 1.0,N-HCl), $[\alpha]_D^{33}$ -51.5°(c 1.00,EtOH). Literature values[6]: mp 156-160°C, $[\alpha]_D^{30}$ +34(c 3.5,N-HCl), $[\alpha]_D^{26}$ -47°(c 3.0,EtOH).

A typical procedure is exemplified by the reduction of acetophenone. To a solution of (R)-1(126 mg,1.21 mmol) in ether(7.5 ml) was added an 0.085 M ethereal solution of LAH(8.2 ml,0.70 mmol) dropwise with stirring under nitrogen at -5°C. On addition of the LAH solution, hydrogen gas evolved and a white precipitate appeared. After adding the LAH solution the mixture was stirred for half an hour at that temperature, then the content chilled to -72°C. To this was added a solution of acetophenone(103 mg, 0.86 mmol) in ether(3.5 ml). The mixture was stirred for 4.8 h at this temperature and then quenched by adding 5 ml of water. The ether layer was separated, washed with 6N HCl and brine successively and dried over Na_2SO_4. After removing the ether, the residue was analyzed to determine the product yield by means of glpc and the pure product was isolated by preparative glpc in order to measure the optical rotation. The hydrochloric acid solution from the ether layer was made strongly basic with aqueous NaOH and after the usual workup, 1 was recovered with a yield of over 80 %. In every case no decrease of the specific rotation of the recovered 1 was observed, showing no racemization occured during the reaction.

The results are shown in Table 1. The addition order of the reactants in preparing the reagent affected O.Y. of the product, suggesting a different complex reagent was formed in each case. Comparing exp. 2 to exp. 3, it is clear that the addition of LAH solution into the amine is preferable to the reverse in O.Y. An effect of the molar ratio of LAH to 1 on O.Y. was also examined with reagent B. The optical yield increased as the ratio decreased, although the synthetic yield (S.Y.) decreased. Temperature played a significant role in the preparation condition. The reduction was tried with each of reagent A, B and C prepared at 20°C, -5°C and -40°C, respectively. We can describe some properties of the reagents as follows: 1) Reagent A is ineffective for the enantioselective reduction. 2) B is effective in the case of not bulky ketones, such as acetophenone, and propiophenone, but ineffective with a bulky one like pivalophenone. 3) C is effective with pivalophenone, whereas it is less effective with acetophenone, and propiophenone. Futhermore, C has more active hydrogens available for the reduction (including selective and non-selective) than A and B.

From the above findings it can be assumed that at least three kinds of the hydride complexes formed depending mainly on the temperature at which they were prepared. Each structure and function has to be clarified to account for these results. An approach to these problems, together with further efforts to improve the O.Y. are now in progress.

Table 1 Asymmetric Reduction of Prochiral Ketones with Chiral Hydride Reagent[a)]

Exp	Substrate	(mmol)	Molar Ratio Subst.: LAH : 1			Config. of 1	Hydride Reagent[b)]	Product S.Y.[c)] (%)	Product O.Y.[d)] (%)	Product Config.
1	$CH_3COC_6H_5$	0.78	0.6	1.0	0.9	(R)	B	85.6	16.5	(R)
2		1.24	0.9	1.0	1.3	(R)	B	73.4	35.5	(R)
3		1.24	0.9	1.0	1.3	(R)	B'	59.4	20.6	(R)
4		1.62	1.1	1.0	1.7	(S)	B	51.2	44.0	(S)
5[e)]		0.86	1.2	1.0	1.7	(R)	B	49.6	45.7	(R)
6		1.62	2.4	1.0	3.4	(S)	B	25.2	43.1	(S)
7		0.77	1.4	1.0	2.1	(R)	C	100	19.4	(R)
8		1.64	0.3	1.0	0.4	(R)	A	100	0	
9		1.64	0.6	1.0	0.8	(R)	A'	80.3	0	
10		1.64	1.2	1.0	1.7	(R)	A'	36.1	0	
11	$CH_3CH_2COC_6H_5$	0.75	1.1	1.0	1.7	(R)	B	41.3	52.5	
12		0.75	1.3	1.0	2.1	(R)	C	100	11.7	
13	$(CH_3)_2CHCOC_6H_5$	0.80	1.1	1.0	1.7	(R)	B	(33.5)	32.5	(R)
14	$(CH_3)_3CCOC_6H_5$	0.77	1.1	1.0	1.7	(R)	B	(54.5)	0	
15		0.78	1.4	1.0	2.1	(R)	C	100	54.3	(S)
16		0.78	1.4	1.0	2.1	(R)	C'	100	37.2	(S)
17	$CH_3COC_{10}H_7(\beta)$	0.82	1.2	1.0	1.7	(R)	B	(17.5)	14.0	(R)
18	$C_6H_5COCO_2C_2H_5$	0.76	1.1	1.0	1.7	(R)	B	(23.0)	31.2	(S)

a) All reductions were done at -72 to -68°C for 2 h unless otherwise noted.

b) Hydride reagents A, B, C and C' were prepared as follow: into ethereal solution of the amine was added LAH solution at the following temperature ; 20°C (A), -5°C (B), -40°C (C) and -20°C (C'). In the cases of A' and B', the reversed addition sequence was used at 20°C (A') and -5°C (B').

c) S.Y. was determined by glpc. The values in parenthesis represent the yield of isolated products by preparative glpc.

d) O.Y.'s were calculated on the basis of the following specific rotations: (R)-(+)-C_6H_5-$CH(OH)CH_3$, $[\alpha]_D^{23}$+45.5°(MeOH)(Ref. 7); (-)-$C_6H_5CH(OH)CH_2CH_3$, $[\alpha]_D^{21}$-47.03°(acetone)(Ref. 8); (R)-(+)-$C_6H_5CH(OH)CH(CH_3)_2$, $[\alpha]_D^{23}$+48.3°(ether)(Ref. 9); (R)-(+)-$C_6H_5CH(OH)C(CH_3)_3$, $[\alpha]_D^{20}$ +36.2°(ether)(Ref. 10); (R)-(+)-β-$C_{10}H_7CH(OH)CH_3$, $[\alpha]_D$+41.3°(EtOH)(Ref. 11); (S)-(+)-C_6H_5-$CH(OH)CO_2C_2H_5$, $[\alpha]_D^{25}$+126.2°($CHCl_3$)(Ref. 12).

e) Reaction time: 4.8 h.

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