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CHIRAL HYDRIDE REAGENTS CONTAINING (R/S)-2,2'-DIHYDROXY-6,6'-DIMETHYLBIPHENYL FOR REDUCTION OF ALKYL PHENYL KETONES

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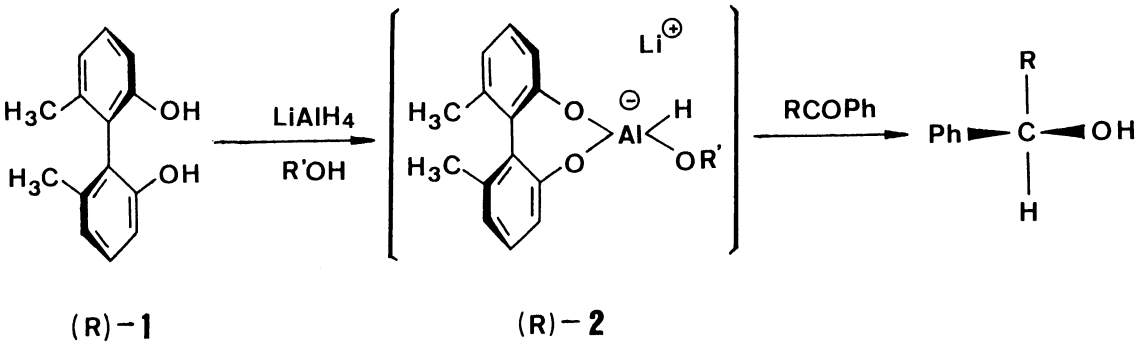
Chiral hydride reagents for asymmetric reduction were prepared from $LiAlH_4$, optically pure 2,2'-dihydroxy-6,6'-dimethylbiphenyl (1), and an achiral alcohol. They showed high enantioface discrimination in the reduction of prochiral alkyl phenyl ketones. The configuration of preferentially formed enantiomer always agreed with that of 1 used for the reagents. Further, polymeric reagents containing (R)-1 moiety were prepared and their behavior in the reduciton was described also.

Recently asymmetric reduction of prochiral ketones by using chiral hydride reagents has been the focus of much research effort. These reagents have been prepared in general by modifying metal hydrides such as $LiAlH_4$, borane, and $NaBH_4$ *etc*. with several kinds of chiral compounds.[1)] Extremely high enantioface discrimination has been reported by Noyori *et al*.[1a)] and Mukaiyama *et al*.[1b)]

During the course of our investigation of the application of axially dissymmetric biphenyl compounds to asymmetric synthesis, we have reported the effective reduction of prochiral alkyl phenyl ketones with $LiAlH_4$/2,2'-diamino-6,6'-dimethylbiphenyl[2a)] and borane/1/achiral amine systems.[2b)] We describe herein similar reduction as above with a chiral reagent prepared *in situ* from $LiAlH_4$, optically pure 1 and an achiral alcohol.

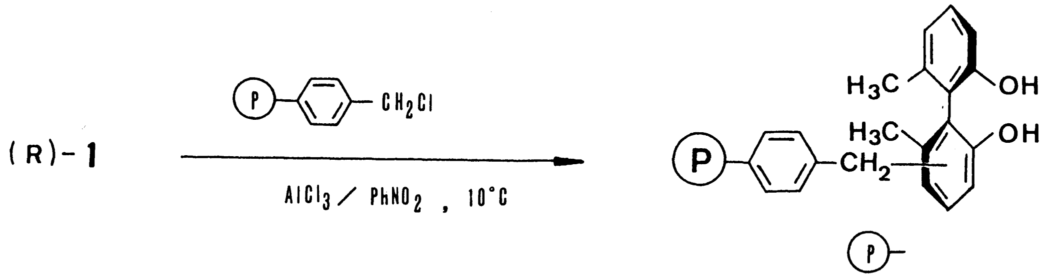


Scheme 1.

Mixing equimolar amounts of $LiAlH_4$, achiral alcohol and (R)-1 in tetrahydrofuran (THF) afforded a white, cloudy mixture, presumably containing a composition indicated in **Scheme 1**. This is quite similar to the binaphthol-modified aluminum hydride reagent reported by Noyori *et al*.1a) The reduction of alkyl phenyl ketones by using (R)-2 gave high optical yields of as much as 89-98% enantiomer excess under certain conditions.

The preparation and optical resolution of chiral ligand 1 were previously described.2b) The procedure for the reduction of acetophenone (Run 9) is illustrated. A 1.98 M solution of ethanol in THF (2.6 ml, 5.15 mmol) was added to a standardized THF solution of $LiAlH_4$ (2.4 ml, 5.09 mmol) at -10 °C under nitrogen atmosphere. Then a solution of 1.10 g (5.13 mmol) of (R)-1 in 10 ml of THF was added slowly at this temperature. On addition of (R)-1, two molar equivalents of hydrogen gas evolved and the reaction mixture became white and cloudy. After stirring this at 20 °C for 1 h followed by cooling to -100 °C, 2.6 ml of 0.97 M solution of acetophenone (2.52 mmol) in THF were added slowly. The reaction mixture was stirred at -100 °C for 3 h and then -78 °C for 16 h, and hydrolyzed by the addition of diluted hydrochloric acid. Ether extracts were washed with 1 N aqueous solution of sodium hydroxide. Removal of the solvent followed by bulb-to-bulb distillation gave an oil, which contained 1-phenylethanol in 52% yield by GLPC analysis. The alcohol was isolated by preparative GLPC or TLC on silicagel (benzene). The pure sample gave $[\alpha]^{25}_{D}$ +41.1 ° (*c* 4.56, MeOH), 92% enantiomer excess of (R)-antipode. More than 90% of (R)-1 was recovered from the alkaline layer by usual workup without noticeable racemization.

Polymer-supported ligands were prepared according to **Scheme 2**. Soluble (number-average molecular weight = 3.0×10^4) and insoluble (cross-linked with 2% divinylbenzene) polystyrenes (PS) were chloromethylated by the reported procedure.3) (R)-1 was bound onto the resulting polymers under ordinary *Friedel-Crafts* alkylation conditions. Usual workup for purification followed by drying *in vacuo* afforded soluble and insoluble polymer-supported ligands [(R)-1a and (R)-1b, respectively].4) When the polymer reagents were used, a longer reaction time was necessary to get a comparable chemical yield (C.Y.). In the case of (R)-1a, additional 50 ml of THF were used in order to make the reaction system being fluidal. After quenching the reaction, the mixture was poured into a large amount of methanol and the precipi-



(R)-1a	soluble PS
(R)-1b	insoluble PS

Scheme 2.

Table 1. Reduction of Alkyl Phenyl Ketones with $LiAlH_4$ Complexes Containing Chiral Dihydroxybiphenyl (1) and Achiral Alcohol[a)]

Run	RCOPh R	Chiral ligand	R'OH R'	Reaction conditions Temp/°C	Time/h	Alcohol produced CY/%[b)]	$[\alpha]^{25}_D$/°	OY/% (config.)[c)]
1	CH_3	(R)-1	—	-78	5	79	+1.1	2 (R)
2		(R)-1	CH_3	-78	5	55	+31.9	70 (R)
3		(R)-1	C_2H_5	0	2	75	+33.1	73 (R)
4		(S)-1	C_2H_5	-10	3	77	-32.8	72 (S)
5		(R)-1	C_2H_5	-78	5	70	+35.7	79 (R)
6[d)]		(R)-1	C_2H_5	-78	5	71	+9.4	21 (R)
7		(R)-1	$i\text{-}C_3H_7$	-78	5	60	+18.7	41 (R)
8		(R)-1	$t\text{-}C_4H_9$	-78	5	70	+16.8	37 (R)
9[e)]		(R)-1	C_2H_5	-100 -78	3 16	52	+41.8	92 (R)
10[f)]		(R)-1a	—	0	2	49	+12.7	28 (R)
11[f)]		(R)-1a	C_2H_5	-10	20	63	+17.9	39 (R)
12		(R)-1b	—	-10	20	81	+7.0	15 (R)
13		(R)-1b	C_2H_5	-10	20	64	+8.1	18 (R)
14		(R)-1b	C_2H_5	-78	24	12	*n.d.*	
....								
15[e)]	C_2H_5	(R)-1	C_2H_5	-100 -78	4 16	39	+41.6	89 (R)
16[e)]	$n\text{-}C_3H_7$	(R)-1	C_2H_5	-100 -78	4 16	60	+44.2	98 (R)

a) The molar ratio of ketone, $LiAlH_4$, 1, and achiral alcohol was 1:2:2:2. When achiral alcohol was not added, the ratio was 1:2:2. b) Chemical yields were determined by GLPC. c) Optical yields were evaluated on the basis of the following specific rotations: (S)-1-phenylethanol, $[\alpha]^{23}_D$ +45.5 ° (MeOH) reported by R.Huisgen and C.Ruchardt, *Liebigs Ann. Chem.*, 601, 31 (1956); (S)-1-phenylpropanol, $[\alpha]^{21}_D$ -47.03 ° (acetone) reported by K.Kwart and D.P.Hoster, *J. Org. Chem.*, 32, 1896 (1967); (S)-1-phenylbutanol, $[\alpha]^{22}_D$ -45.2 ° (*c* 4.81, benzene) reported in Ref. 1a. d) After preparinq the complex, the reaction mixture was stirred at 50 °C for 1 h. e) The reaction was carried out at -100 °C for 3-4 h and then at -78 °C for 16 h. f) 50 ml of THF were added.

tated polymer was separated and washed repeatedly with the solvent. The filtrate was worked up in a similar manner as above. On the other hand, the reagent from insoluble (R)-1b was removed simply by filtration and washed throughly with methanol.

The results are summerized in **Table 1.** The reduction of acetophenone, one of the most used model compounds, was carried out by using (R)-2 (R'=C_2H_5). The optical yield (O.Y.) increased with lowering the reaction temperature (Runs 2-4). Cooling to -100 °C in the initial stage of the reaction (Run 6) brought about an additional increase of O.Y. at a slight expense of C.Y. In the case of acetophenone the highest O.Y. of 92% was obtained. The configuration of preferentially formed enantiomer always agreed with that of 1 used for the reagents.

The effect of additive alcohol on the asymmetric selection was examined at -78 °C by using four kinds of alcohols. Smaller alcohols such as methanol and ethanol showed higher selections than bulkier alcohols like *i*-propanol and *t*-butanol. Absence of any alcohol affected seriously the selection and resulted in the extremely low O.Y. of only 2% as likely as the case of the binaphthol-modified reagent.[1a] This may be ascribed to *non*-selective reduction caused by $LiAlH_4$ which was formed by the disproportionation of intermediate biphenyldioxyaluminum dihydride as T.H.Johnson *et al.* pointed out.[5] On the other hand, when an equimolar alcohol was added, the major reducing agent would be the monohydride like as (R)-2. This is supposed to be far less labile compared to the dihydride at lower temperature, thus resulting in quite a high selection. In the case of polymeric reagent, (R)-1a or (R)-1b, the effect of additive alcohol on the selection was found to be only small. This fact suggests that the disproportionation of the dihydride was strongly retarded due to immobility of the (R)-1 moiety bound to the polymer chain, especially to the cross-linked chain.

The reduction of propiophenone and butyrophenone with (R)-2 ($R'=C_2H_5$) at -100 °C afforded also high O.Y.s of 89 and 98%, respectively (Runs 15 and 16).

References

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2) a) H.Suda, M.Motoi, M.Fujii, S.Kanoh, and Y.Yoshida, *Tetrahedron Lett.*, 20, 4565 (1979); b) H.Suda, S.Kanoh, N.Umeda, T.Nakajo, and M.Motoi, *Tetrahedron Lett.*, 24, 1513 (1983).

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4) IR spectra of these polymers showed no absorption ascribable to aromatic ether linkage. (R)-1a: Anal. Found: C, 88.58; H, 7.20; Cl, 0.00%. Active hydrogen;[6] 2.79 mmol of H/g. The content of (R)-1 unit/g of polymer was evaluated to 1.3 and 1.4 mmol based on the elemental analysis and the determination of active hydrogen, respectively. (R)-1b: Active hydrogen; 3.41 mmol of H/g. Although a part of the chloromethyl groups remained unreacted, 1.7 mmol of (R)-1 unit/g of resin was introduced.

5) T.H.Johnson and G.Rangarajan, *J. Org. Chem.*, 44, 3966 (1979).

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