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ASYMMETRIC REDUCTION OF PROCHIRAL CYCLIC KETONES WITH LITHIUM ALUMINUM HYDRIDE PARTIALLY DECOMPOSED BY (1R,2S)-(-)-N-METHYLEPHEDRINE AND 2-ALKYLAMINOPYRIDINE

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The title chiral hydride was found to reduce prochiral cyclic ketones, affording the corresponding optically active cyclic alcohols in high optical(max. 98%ee) yields.

The asymmetric reduction of prochiral ketones with chiral hydride reagents has been extensively studied in recent years.[1,2] While high optical yields have been achieved in the asymmetric reductions of prochiral open-chain ketones,[2-4] the number of the chiral hydrides which can produce highly optically active cyclic alcohols from prochiral cyclic ketones such as 2-cyclohexen-1-one and α- or β-tetralone seems to be quite limited.[5,6]

We wish to report here that the chiral hydride reagent prepared by modifying lithium aluminum hydride(LAH) with (1R,2S)-(-)-N-methylephedrine[(-)-N-methylephedrine][2] and 2-alkylaminopyridine[7] can reduce prochiral cyclic ketones, giving the corresponding optically active cyclic alcohols in high optical(max. 98%ee) yields.

In order to find out the best chiral hydride and to optimize the reduction conditions, alkyl substituents of 2-alkylaminopyridines used as additives, reaction solvents, and reaction temperatures were first examined by employing 2-cyclohexen-1-one as a reduction substrate. As shown in Table 1, it is clearly disclosed that when 2-cyclohexen-1-one is treated with the chiral hydride, prepared by successive decomposition of LAH with (-)-N-methylephedrine[2] and 2-ethylaminopyridine,[7] in ether at -78 °C for 3 h, (R)-(+)-2-cyclohexen-1-ol, 98%ee, can be obtained in 81% yield with a 9% recovery of the starting material.

A typical experimental procedure is represented for run 2 in Table 1: An ethereal solution(14 ml) of (-)-N-methylephedrine(mp 85-86 °C, $[\alpha]_D^{20}$ -30.2°(c 4.48, MeOH))[2] (1.94 g, 10.8 mmol) was added to a suspension of LAH(376 mg, 9.9 mmol) in ether(8.5 ml), and the mixture was heated at reflux for 1 h with stirring. An ethereal solution(8.5 ml) of 2-ethylaminopyridine[7] (2.64 g, 21.6 mmol) was added to the ethereal suspension prepared above, and the mixture was further heated at reflux for 1 h with stirring to give a yellowish green suspension of the reducing agent. A solution of 2-cyclohexen-1-one(288 mg, 3.0 mmol) in ether(3 ml) was gradually added to the ethereal suspension of the reducing agent cooled at -78 °C,

TABLE 1. ASYMMETRIC REDUCTION OF 2-CYCLOHEXEN-1-ONE WITH LITHIUM ALUMINUM HYDRIDE PARTIALLY DECOMPOSED BY (-)-N-METHYLEPHEDRINE AND 2-ALKYLAMINOPYRIDINE[a]

	Reaction conditions			(R)-(+)-2-Cyclohexen-1-ol		
Run	Alkyl group of 2-alkylaminopyridine	Solv.	Temp °C	Chemical yield/%[b]	Optical rotation[c] $[\alpha]_D^{20}$ (c, $CHCl_3$)	Optical yield/%[d]
1[e]	Me	Et_2O	-78	17[f]	+69° (0.37)	62
2	Et	Et_2O	-78	81 (9)	+110° (0.60)	98
3[e]	n-Pr	Et_2O	-78	67 (4)	+103° (0.58)	92
4[e]	i-Pr	Et_2O	-78	49 (7)	+35° (0.48)	31
5[e]	$PhCH_2$	Et_2O	-78	60 (2)	+103° (0.58)	92
6	Et	THF	-78	56 (14)	+85° (0.69)	76
7	Et	PhMe	-78	7 (23)	-[g]	-[g]
8	Et	Et_2O	-45	77 (9)	+104° (0.58)	93
9	Et	Et_2O	0	75[f]	+93° (0.72)	83
10	Et	Et_2O	35	75 (10)	+82° (0.80)	73

a) All reactions were carried out using LAH (3.3 equiv.) partially decomposed with (-)-N-methylephedrine (3.6 equiv.) and 2-alkylaminopyridine (7.2 equiv.) for 3 h. b) Calculated for the sample purified by column chromatography. Numbers in parentheses show the recovery yields of 2-cyclohexen-1-one. c) Measured on the sample purified by bulb-to-bulb distillation. d) Optically pure (S)-(-)-2-cyclohexen-1-ol gives $[\alpha]_D^{20}$ -112.0° (c 0.60, $CHCl_3$). S. Yamada, N. Takamura, and T. Mizoguchi, Chem. Pharm. Bull., 23, 2539 (1975). e) (-)-N-Methylephedrine (3.4 equiv.) and 2-alkylaminopyridine (6.8 equiv.) were used for decomposing LAH (3.3 equiv.). f) Recovery yield of 2-cyclohexen-1-one was not determined. g) Measurement of the optical rotation was not performed.

and the mixture was stirred at the same temperature for 3 h. After methanol (0.5 ml) was added to quench the reduction, the reaction mixture was stirred at -78 °C for 5 min. The mixture was further diluted with 3 mol dm^{-3}-HCl (35 ml), then extracted with ether. The combined ethereal extracts were washed successively with 1% HCl, satd. $NaHCO_3$, and satd. NaCl, and dried over anhyd. $MgSO_4$. Filtration and concentration *in vacuo* gave an oily residue (340 mg) which was purified by column chromatography (SiO_2, $CHCl_3$-Et_2O 19:1) to afford 2-cyclohexen-1-one (25 mg, 9%) and (R)-(+)-2-cyclohexen-1-ol (239 mg, 81%). (R)-(+)-2-Cyclohexen-1-ol was further purified by bulb-to-bulb distillation, giving the pure sample as a colorless oil (224 mg, 76%), bp 150 °C (100 mmHg) (bath temp), $[\alpha]_D^{20}$ +110° (c 0.60, $CHCl_3$).

Practical aspects of the asymmetric reduction might be emphasized by the facts that, being different from the reported chiral hydrides,[3-6] a suspension of LAH in ether is usable for preparing our chiral reagent, and that the reductions even at -45 °C and 0 °C can afford 93% and 83% optical yields of (R)-(+)-2-cyclohexen-1-ol, respectively.

The developed reducing agent was next applied to the asymmetric reduction of various structural types of prochiral cyclic ketones. The results summarized

TABLE 2. ASYMMETRIC REDUCTION OF VARIOUS PROCHIRAL KETONES WITH LITHIUM ALUMINUM HYDRIDE PARTIALLY DECOMPOSED BY (-)-N-METHYLEPHEDRINE AND 2-ETHYLAMINOPYRIDINE[a]

Run	Substrate	Optically active cyclic alcohols			
		Chemical yield/%[b]	Optical rotation[c] $[\alpha]_D^{20}$ (c, $CHCl_3$)	Optical yield/%	Absolute confign.
1[d]	2-Methyl-2-cyclohexen-1-one	82	+130° (1.39)	96[e,f]	(R)[g]
2[d]	3-Methyl-2-cyclohexen-1-one	57 (24)	+87° (0.46)	90[h]	(R)[h]
3	2-Cyclohepten-1-one	74 (18)	+21.3° (2.43)	73[e]	(R)[i]
4	α-Tetralone	93 (7)	-31.4° (2.64)	96[j]	(R)[k]
5	1-Indanone	86 (12)	-28.0° (2.02)	81[l]	(R)[k]
6	β-Tetralone	84 (15)	+68.0° (1.61)[m]	93[f]	(R)[g,n]

a) All reactions were carried out under the same condition as for the asymmetric reduction of 2-cyclohexen-1-one (Table 1, Run 2). b,c) See Table 1 footnotes b,c). d) The reaction mixture was worked up under the basic condition. See the text. e) Determined by measuring NMR spectrum of the corresponding acetate in the presence of Eu(hfc)$_3$. f) Determined by measuring NMR spectrum of the diastereomeric (R)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) esters in the presence of Eu(fod)$_3$. g) Tentatively assigned based on NMR spectrum of the diastereomeric (R)-MTPA esters measured in the presence of Eu(fod)$_3$. S. Yamaguchi, F. Yasuhara, and K. Kabuto, Tetrahedron, 32, 1363 (1976). h) Optically pure (R)-(+)-3-methyl-2-cyclohexen-1-ol gives $[\alpha]_D^{20}$ +96.3±0.3° (c 0.423, $CHCl_3$). K. Mori, S. Tamada, M. Uchida, N. Mizumachi, Y. Tachibana, and M. Matsui, Tetrahedron, 34, 1901 (1978). i) Tentatively assigned by considering the result for asymmetric reduction of 2-cyclohexen-1-one. j) Optically pure (+)-1,2,3,4-tetrahydro-1-naphthol shows $[\alpha]_D^{17}$ +32.65° (c 2.5, $CHCl_3$). A.G. Davies and A.M. White, J. Chem. Soc., 1952, 3300. k) See Ref. 2. l) Optically pure (+)-indan-1-ol gives $[\alpha]_D^{20}$ +34.4° (c 1.97, $CHCl_3$). W. Hückel and F. Mössner, Liebigs Ann. Chem., 637, 57 (1960). m) Measured at 19 °C in ethanol. n) H. Arakawa, N. Torimoto, and Y. Masui, Tetrahedron Lett., 1968, 4115.

in Table 2 clearly show that the reduction of these cyclic ketones proceed highly enantioselectively in a manner similar to the case for 2-cyclohexen-1-one. Since optically active (R)-(+)-2- and 3-methyl-2-cyclohexen-1-ol were found to be readily racemizable under the acidic workup condition (*vide supra*), the reduction was quenched by successive addition of methanol, water, 15% NaOH, and water, and an oily mixture, obtained by filtration and concentration *in vacuo*, was separated by column chromatography.

Finally, with the aim to further evaluate the characteristics of the exploited chiral hydride, the asymmetric reductions of typical open-chain ketones such as acetophenone and 4-phenyl-3(E)-buten-2-one were attempted. Treatments of these ketones under the same condition as for 2-cyclohexen-1-one (Table 1, Run 2) were found to readily give (R)-(+)-1-phenylethanol, $[\alpha]_D^{20}$ +28.2° (c 2.23, CH_2Cl_2), 54%ee,[8] and (R)-(+)-4-phenyl-3(E)-buten-2-ol, $[\alpha]_D^{20}$ +13.3° (c 4.80, $CHCl_3$), 34%ee,$^{9)}$ in 97% and 89% yields, respectively. These results obviously disclose that our new chiral reagent is especially useful for the asymmetric reduction of prochiral cyclic ketones rather than that of prochiral open-chain ketones.

Considering various novel aspects including high optical yield, operational simplicity, and uses of readily available chiral sourse and additive, the developed chiral hydride should have a high potential for practical asymmetric synthesis of optically active cyclic alcohols which are anticipated to be versatile synthetic blocks in natural product synthesis.

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6) After our chiral hydride reagent had been developed, Fujisawa, *et al*. reported that the chiral hydride prepared from LAH and (S)-4-anilino-3-methylamino-1-butanol could reduce 2-cyclohexen-1-one in a high optical(max. 100%ee at -100 °C) yield. We thank Prof. Fujisawa for letting us see a copy of his paper in advance of publication. T. Sato, Y. Gotoh, Y, Wakabayashi, and T. Fujisawa, Tetrahedron Lett., 24, 4123(1983).

7) 2-Alkylaminopyridines other than 2-benzylaminopyridine were prepared from 2-aminopyridine by successive formylation(Ac_2O-HCOOH), alkylation(NaH-MeI or EtBr), and hydrolysis(aq. HCl), or by direct alkylation(NaH-EtBr, n-PrI, or i-PrI) followed by chromatographic separation. Preparation of 2-benzylaminopyridine was performed by reductive alkylation of 2-aminopyridine(PhCHO-HCOOH).

8) Optically pure (S)-(-)-1-phenylethanol gives $[\alpha]_D^{22}$-52.5°(c 2.27, CH_2Cl_2). U. Nagai, T. Shishido, R. Chiba, and H. Mitsuhashi, Tetrahedron, 21, 1701(1965).

9) (S)-(-)-4-Phenyl-3(E)-buten-2-ol showing $[\alpha]_D^{20}$-18.6°(c 5.26, $CHCl_3$),$^{2)}$ was determined to be 47%ee by measuring NMR spectrum of the corresponding acetate in the presence of $Eu(hfc)_3$. Therefore, the optical rotation of optically pure (S)-(-)-4-phenyl-3(E)-buten-2-ol can be calculated as $[\alpha]_D^{20}$-39.6°($CHCl_3$). The similar rotation value was also recorded by Fujisawa, *et al*.$^{6)}$

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