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Asymmetric Reduction of 4-Phenyl-3(*E*)-buten-2-one by Using Lithium Aluminum Hydride Partially Decomposed with (−)-*N*-Methylephedrine and Achiral Secondary Amine

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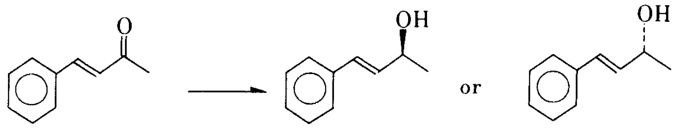
The optical rotation of optically pure (*S*)-(−)-4-phenyl-3(*E*)-buten-2-ol ((*S*)-(−)-**2**) was determined on the basis of nuclear magnetic resonance (NMR) spectral measurements of the acetate in the presence of a chiral shift reagent. Our former result on the asymmetric reduction of 4-phenyl-3(*E*)-buten-2-one (**1**) had to be corrected.

The title chiral hydride prepared by using diphenylamine or 2-anilinopyridine as an achiral additive was found to reduce **1**, affording (*S*)-(−)- or (*R*)-(+)-**2** in 66% or 53% optical yield.

Keywords——asymmetric reduction; lithium aluminum hydride; (−)-*N*-methylephedrine; (*S*)-(−)-4-phenyl-3(*E*)-buten-2-ol; (*R*)-(+)-4-phenyl-3(*E*)-buten-2-ol; 4-phenyl-3(*E*)-buten-2-one; *N*-ethylaniline; diphenylamine; 2-anilinopyridine; secondary amine

In our previous report,[1] the asymmetric reduction of 4-phenyl-3(*E*)-buten-2-one (benzalacetone) (**1**) by the use of lithium aluminum hydride (LAH) partially decomposed with (1*R*,2*S*)-(−)-*N*-methylephedrine [(−)-*N*-methylephedrine] and *N*-ethylaniline was claimed to afford (*S*)-(−)-4-phenyl-3(*E*)-buten-2-ol ((*S*)-(−)-**2**), $[\alpha]_D^{20}$ $-24.2°$ ($c=5.00$, chloroform), in 98% yield. The optical yield of (*S*)-(−)-**2** was calculated as 98%ee based on the assumption that (*R*)-(+)-**2** having the maximum rotation value, $[\alpha]_D^{rt}+24.7°$ ($c=5.000$, chloroform),[2] was optically pure.[3]

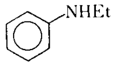
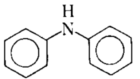
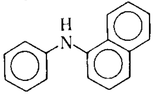
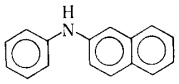
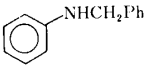
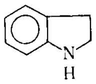
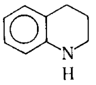
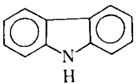
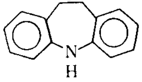
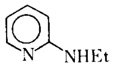
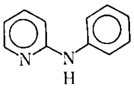
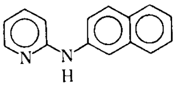
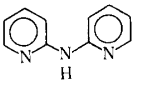
Since it was recently disclosed that (*S*)-(−)-**2** having $[\alpha]_D^{23}$ $-29.7°$ ($c=5.01$, chloroform) and $[\alpha]_D$ -35.2 ± 1.1 (chloroform) should be 72%[4] and 100%[5] optically pure, respectively, we re-examined the asymmetric reduction of **1**. It was found that our former result could not be reproduced and that the asymmetric reduction usually gives (*S*)-(−)-**1** showing a lower optical rotation, $[\alpha]_D^{20}$ $-18.6°$ ($c=5.26$, chloroform). By using the reported method,[4,5] the optical purity of this sample was determined to be 47%ee by measuring the nuclear magnetic resonance (NMR) spectrum of the acetate in the presence of tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III)[Eu(hfc)$_3$]. Accordingly, the optical rotation of optically pure (*S*)-(−)-**2** can be estimated as $[\alpha]_D^{20}$ $-39.6°$ (chloroform).



Chart

Optically active allylic alcohols ((*S*)-(−)- and (*R*)-(+)-**2**) are frequently utilized as standard chiral compounds for synthetic studies of optically active compounds and for studies

Table I. Asymmetric Reduction of 4-Phenyl-3(*E*)-buten-2-one with LAH Partially Decomposed with (−)-*N*-Methylephedrine and Achiral Secondary Amine[a]

Run	Achiral amine additive[b]	Optically active 4-phenyl-3(*E*)-buten-2-ol (**2**)			
		Chemical yield (%)[c]	$[\alpha]_D^{20}$ (°) (*c*, $CHCl_3$)[d]	Optical yield (%)[e]	Absolute confign.[e]
1[f]		94	−18.6 (5.26)	47	(*S*)
2		97	−26.0 (6.86)	66	(*S*)
3		86	−25.0 (4.26)	63	(*S*)
4		88	−25.6 (5.00)	65	(*S*)
5		79	−7.3 (4.94)	18	(*S*)
6		62	−7.1 (4.10)	18	(*S*)
7		94	−18.0 (5.20)	45	(*S*)
8		20 (43)	−20.8 (1.66)	53	(*S*)
9		64	+0.7 (4.00)	2	(*R*)
10[g]		89	+13.3 (4.80)	34	(*R*)
11		79	+20.9 (5.04)	53	(*R*)
12		76 (15)	+17.8 (4.64)	45	(*R*)
13		15 (44)	−1.2 (6.50)	3	(*S*)

a) All reactions were carried out using LAH (3.3 eq) partially decomposed with (−)-*N*-methylephedrine (3.6 eq) and achiral secondary amine additive (7.2 eq) in ether at −78 °C for 3 h.

b) Achiral secondary amines except for 2-ethylaminopyridine[8] and 2-*β*-naphthylaminopyridine[9] are all commercially available.

c) Optically active **2** which contains some impurities was purified by column chromatography ($CHCl_3$, then $CHCl_3$–EtOAc (4 : 1)). The chemical yield was calculated for the pure sample.

d) Measured on a sample further purified by bulb-to-bulb distillation.

e) Optically pure (*S*)-(−)-**2** gives $[\alpha]_D^{20}$ −39.6° ($CHCl_3$).

f) LAH (3.3 eq) partially decomposed with (−)-*N*-methylephedrine (3.4 eq) and *N*-ethylaniline (6.8 eq) was used. See ref. 1 and the experimental section.

g) Reported in ref. 8.

of reaction mechanisms.5—7) Therefore, the asymmetric reduction of **1** was further examined by employing chiral hydrides produced by the use of various types of achiral secondary amines as additives. The results are summarized in Table I.

When **1** was treated with the chiral hydride prepared by using diphenylamine as an additive, (*S*)-(−)-**2**, 66% ee, was obtained in 97% yield (Table I, run 2), while the chiral hydride containing 2-anilinopyridine as an additive produced (*R*)-(+)-**2**, 53% ee, in 79% yield (Table I, run 11). The chiral hydride prepared by using 2-ethylaminopyridine as an additive, which had been developed as a reducing agent suitable for achiral cyclic ketones,8) was found to give a poor result (Table I, run 10).

While further improvement of the optical yield is required, our new reagents might be convenient for preparing an enantiomeric pair of optically active **2** with 50—70% ee.

Experimental10)

2-β-Naphthylaminopyridine——Prepared from 2-aminopyridine and β-naphthol according to the reported method.9) mp 132—133 °C (lit.,9) mp 135 °C).

(*S*)-(−)-4-Phenyl-3(*E*)-buten-2-ol ((*S*)-(−)-2)——2) Table I, Run 1: Treatment of **1** in the reported manner1) gave (*S*)-(−)-**2** as a colorless oil in 94% yield after extractive isolation and purification by column chromatography (EtOAc–C_6H_{14} (1 : 4)→EtOAc–C_6H_{14}(1 : 1)). The optical rotation was recorded on a sample further purified by bulb-to-bulb distillation, bp 150 °C (5 mmHg) (bath temp.), $[\alpha]_D^{20}$ −18.6° (c=5.26, $CHCl_3$). Infrared (IR) and NMR spectra of this oil were identical with those reported.1) The oily alcohol was treated with Ac_2O–Py, giving (−)-4-phenyl-3(*E*)-buten-2-yl acetate as a colorless oil in quantitative yield, bp 150 °C (5 mmHg) (bath temp.), $[\alpha]_D^{20}$ −80.4° (c=5.44, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1740 (ester). NMR ($CDCl_3$) δ: 1.40 (3H, d, J=6 Hz, $C\underline{H}_3CH$), 2.05 (3H, s, $C\underline{H}_3CO$), 5.46 (1H, dq, J=each 6 Hz, $C\underline{H}O$), 6.13 (1H, dd, J=15 and 6 Hz, $=C\underline{H}CHO$), 6.55 (1H, d, J=15 Hz, $ArC\underline{H}=$), 7.1—7.5 (5H, m, aromatic protons). MS *m/e*: 190 (M^+), 129, 115. MS. Calcd for $C_{12}H_{14}O_2$ (M^+, *m/e*) 190.0993. Found: 190.1006. The NMR spectrum of this sample measured in the presence of Eu(hfc)$_3$ (the acetate: Eu(hfc)$_3$, 9 : 7) showed the acetyl group signal as two singlets at 5.52 and 5.45 ppm in an integration ratio of 73.6 : 26.4. Therefore, the optical purity of this sample was determined as 47% ee. Based on this value, the optical rotation of optically pure (*S*)-(−)-**1** could be estimated as $[\alpha]_D^{20}$ −39.6° ($CHCl_3$).

b) Table I, Run 2: An ethereal solution (14 ml) of (−)-*N*-methylephedrine (mp 85—86 °C, $[\alpha]_D^{20}$ −30.2° (c=4.48, MeOH)1,8)) (1.94 g, 10.8 mmol) was added to a suspension of LAH (376 mg, 9.9 mmol) in Et_2O (8.5 ml), and the mixture was heated at reflux for 1 h with stirring. An ethereal solution (8.5 ml) of diphenylamine (3.66 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 suspension of the reducing reagent.

A solution of **1** (439 mg, 3.0 mmol) in Et_2O (3 ml) was added to the suspension of the reducing reagent cooled at −78 °C, and the mixture was stirred at the same temperature for 3 h. MeOH (0.5 ml) was added to quench the reduction, then the mixture was diluted with 3 N HCl (30 ml), and extracted with Et_2O. The ethereal extracts were combined and washed successively with satd. NaCl, satd. $NaHCO_3$, and satd. NaCl. Filtration and concentration *in vacuo* gave an yellow oil, which was purified by column chromatography ($CHCl_3$, then $CHCl_3$–EtOAc (4 : 1)) to afford (*S*)-(−)-**2** as a colorless oil (430 mg, 97%). The optical rotation was measured on a sample further purified by bulb-to-bulb distillation (417 mg, 94%), bp 150 °C (5 mmHg) (bath temp.), $[\alpha]_D^{20}$ −26.0° (c=6.86, $CHCl_3$). Since optically pure (*S*)-(−)-**2** gives $[\alpha]_D^{20}$ −39.6° ($CHCl_3$), the optical yield of this sample could be calculated as 66% ee. The spectral (IR and NMR) properties of this sample were identical with those reported.1)

(*R*)-(+)-4-Phenyl-3(*E*)-buten-2-ol ((*R*)-(+)-2)——Table I, Run 11: A similar reaction procedure to that described above was carried out by using 2-anilinopyridine (3.68 g, 21.6 mmol) as an achiral amine additive, giving (*R*)-(+)-**2** as a colorless oil (350 mg, 79%) after extractive isolation and purification by column chromatography ($CHCl_3$, then $CHCl_3$–EtOAc (3 : 1)). Measurement of the optical rotation was performed on a sample further purified by bulb-to-bulb distillation (343 mg, 77%), bp 150 °C (5 mmHg) (bath temp.), $[\alpha]_D^{20}$ +20.9° (c=5.04, $CHCl_3$). The optical yield of this sample was similarly estimated to be 53% ee.

References and Notes

1) *a*) S. Terashima, N. Tanno, and K. Koga, *J. Chem. Soc., Chem. Commun.*, **1980**, 1026; *b*) N. Tanno and S. Terashima, *Chem. Pharm. Bull.*, **31**, 837 (1983).

2) J. Kenyon, S. M. Partridge, and H. Phillips, *J. Chem. Soc.*, **1936**, 85.

3) In order to determine the optical purity of (*S*)-(−)-**2**, measurement of the NMR spectrum of (±)-**2** was carried out in the presence of Eu(hfc)$_3$. Since separation of methyl and/or methine signals of (±)-**2** could not be observed, we assumed the maximum reported value2) to be 100% ee (see footnote 10 in ref. 1*b*).

4) T. Sato, Y. Gotoh, Y. Wakabayashi, and T. Fujisawa, *Tetrahedron Lett.*, **24**, 4123 (1983).
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6) *a*) H. C. Brown and G. G. Pai, *J. Org. Chem.*, **47**, 1606 (1982); *b*) T. Hayashi, T. Hagiwara, M. Konishi, and M. Kumada, *J. Am. Chem. Soc.*, **105**, 7767 (1983); *c*) K. Soai, H. Oyamada, and T. Yamanoi, *J. Chem. Soc., Chem. Commun.*, **1984**, 413.
7) C. Fuganti, P. Grasselli, F. Spreafico, and C. Zirotti, *J. Org. Chem.*, **49**, 543 (1984).
8) *a*) M. Kawasaki, Y. Suzuki, and S. Terashima, *Chem. Lett.*, **1984**, 239; *b*) *Idem, Chem. Pharm. Bull.*, **33**, 52 (1985).
9) N. P. Buu-Hoï, *J. Chem. Soc.*, **1952**, 4346.
10) All boiling points are uncorrected. A Shibata GTO-250R glass tube oven was used for bulb-to-bulb distillation. IR spectral measurements were performed with a JASCO A-202 diffraction grating infrared spectrometer. NMR spectra were measured with a Varian EM 390 spectrometer (90 MHz). Measurements of optical rotations were performed using a Union PM-201 automatic digital polarimeter. All reactions were carried out using anhyd. solvents, and the combined organic extracts obtained in each experiment were dried over anhyd. $MgSO_4$ before filtration and concentration *in vacuo* with a rotary evaporator. Column chromatography was performed using silica gel (SiO_2) as an adsorbent. The following abbreviations are used for solvents and reagents: chloroform ($CHCl_3$), ether (Et_2O), ethyl acetate (EtOAc), lithium aluminum hydride (LAH).