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ASYMMETRIC REDUCTION OF SIMPLE ACHIRAL KETONES WITH LITHIUM ALUMINUM HYDRIDE PARTIALLY DECOMPOSED BY (-)-N-METHYLEPHEDRINE AND N-ETHYLANILINE

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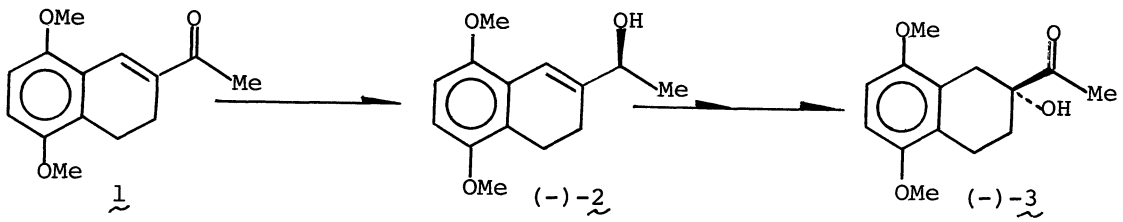
The title asymmetric reduction was found to give the corresponding optically active alcohols in high optical(max. 90% ee) and chemical(max. 100%) yields.

The asymmetric reduction of achiral ketones has been of increasing interests in recent years,[1] and high optical yields have been achieved using lithium aluminum hydride partially decomposed with various types of chiral compounds, as reducing agents.[2,3,4]

We have previously reported the asymmetric synthesis of optically active anthracyclinones,[5] aglycones of anthracycline antibiotics currently attracting much attention because of their promising anti-cancer activity.[6] In the exploited asymmetric synthesis, the novel chiral hydride originally prepared by partially decomposing lithium aluminum hydride with (-)-N-methylephedrine(1 eq) and N-ethylaniline(2 eq), is found to effectively reduce 2-acetyl-5,8-dimethoxy-3,4-dihydronaphthalene(1), giving the desired allylic alcohol((-)-2) in high optical(92% ee) and chemical(100%) yields.[5,7] Direct recrystallization of the reduction product(92% ee) yields optically pure (-)-2 in 87% yield based on 1, which could be elaborated to the optically pure key synthetic intermediate((-)-3) of anthracyclinones.[8]



1 (-)-2 (-)-3

This reduction could fulfill the criteria required for practical asymmetric synthesis, based on its various novel aspects such as high optical and chemical yields, operational simplicity, use of readily available (-)-N-methylephedrine as a chiral source, and simple procedure for recovering the chiral source and the additive for reuse. Therefore, the asymmetric reduction of simple achiral ketones was further attempted to explore general applicability of the newly developed reagent. We have now found that these ketones can be efficiently reduced by the novel chiral hydride in a manner similar to that for 1, to give

the corresponding optically active alcohols whose optical yields compares fairly well with the best results hitherto reported.[2,3,4]

Results for the asymmetric reductions are summarized in Table I. The typical experimental procedures are described for runs 3 and 5.

Run 3: To a stirred suspension of lithium aluminum hydride(206 mg, 5.4 mmole) in ether(10 ml) was added a solution of (-)-N-methylephedrine[10] (1.00 g, 5.56 mmole) in ether(10 ml) over 5 min under argon atmosphere, and the mixture was heated at reflux for 1 hr with stirring. An ethereal solution(10 ml) of N-ethylaniline(1.35 g, 11.1 mmole) was added to the reaction mixture over 5 min, and the stirring was further continued for 1 hr under reflux, giving an ethereal suspension of the reducing agent.

To the stirred ethereal suspension cooled at -78°C in a dryice-acetone bath, was added a solution of acetophenone(360 mg, 3.0 mmole) in ether(10 ml) over 5 min, and the whole was stirred at -78°C for 3 hr. After 1N-HCl(24 ml) was added to the reaction mixture at -78°C and the cooling bath was removed, the stirring was continued for 15 min at room temperature. The ethereal layer was separated, washed successively with 10% HCl and satd. NaCl, then dried over anhyd. $MgSO_4$. Filtration and evaporation in vacuo gave almost pure (S)(-)-1-phenylethanol as a colorless oil(330 mg, 90%), which was directly purified by bulb to bulb distillation, giving the pure sample(317 mg, 87%), bp 160°C(bath temp)(17 mmHg), $[\alpha]_D^{20}$-36.4°(c=7.45, cyclopentane), 84% ee.

The combined acidic phases were made alkaline(pH>11) with 10% NaOH, and extracted with ethyl acetate. The ethyl acetate layers were combined, washed with satd. NaCl, and dried. Filtration and evaporation in vacuo gave a mixture of (-)-N-methylephedrine and N-ethylaniline as a mixture of crystals and oil(2.41 g, ∿100%), which was subjected to bulb to bulb distillation, giving N-ethylaniline as an oil(1.32 g, 98%) and (-)-N-methylephedrine(0.82 g, 82%) without racemization, mp 87.5-89.5°C, $[\alpha]_D^{20}$-29.0°(c=6.50, methanol), 98% ee.[11]

Run 5: A solution of propiophenone(201 mg, 1.5 mmole) in ether(5 ml) was added over 5 min to an ethereal suspension of the reducing agent, prepared from lithium aluminum hydride(103 mg, 2.7 mmole) in completely the same manner as for run 3, at -78°C under argon atmosphere. After the stirring was continued at the same temperature for 3 hr, the reaction mixture was worked up in a way similar to that for run 3, giving an oily evaporation residue. This was purified by preparative tlc(silica gel, dichloromethane), to afford pure (S)(-)-1-phenyl-1-propanol as a colorless oil(196 mg, 96%). The sample further purified by bulb to bulb distillation(bath temp, 175°C; 21 mmHg), weighed 179 mg (88%) and showed $[\alpha]_D^{27}$-41.0°(c=5.58, chloroform), 90% ee.

Results other than that for run 3 were obtained by the same procedure as for run 5. Experiments in runs 1-4 show that the use of 1.8 equivalents of the reducing agent and the reaction temperature of -78°C are enough for the usual asymmetric reduction.[9,12] Since 3.3 equivalents of the reducing agent are required for completing the reduction of 1,[5] this fact discloses that simple ketones could be generally reduced by the exploited reagent more easily than α,β-unsaturated ketones.

Table I Asymmetric Reduction of Simple Achiral Ketones with Lithium Aluminum Hydride Partially Decomposed by (-)-N-Methylephedrine and N-Ethylaniline[a)]

Run	Substrate	Reac. Condition: Molar Eq. of Reagent	Reac. Condition: Temp. °C	Optically Active Alcohols: Chemical Yield (%)[b)]	Optically Active Alcohols: Optical Rotation[c)]	Optical Yield (% ee)	Abs. Confign.
1	PhCOMe	1.2	-78	71	$[\alpha]_D^{20}$-34.5°(c=4.00, cyclopentane)	80[d)]	S
2	PhCOMe	1.8	-78	94	$[\alpha]_D^{20}$-36.2°(c=5.53, cyclopentane)	84[d)]	S
3	PhCOMe	1.8	-78	90[e)]	$[\alpha]_D^{20}$-36.4°(c=7.45, cyclopentane)	84[d)]	S
4	PhCOMe	1.8	-100	86	$[\alpha]_D^{20}$-37.9°(c=5.98, cyclopentane)	88[d)]	S
5	PhCOEt	1.8	-78	96	$[\alpha]_D^{27}$-41.0°(c=5.58, chloroform)	90[f)]	S
6	PhCOi-Pr	1.8	-78	95	$[\alpha]_D^{20}$-37.0°(c=6.95, ether)	78[g)]	S
7	PhCOn-Bu	1.8	-78	100	$[\alpha]_D^{22}$-36.6°(c=5.04, benzene)	80[h)]	S
8	1-indanone	1.8	-78	88	$[\alpha]_D^{20}$+24.4°(c=2.01, chloroform)	71[i)]	S
9	α-tetralone	1.8	-78	96	$[\alpha]_D^{17}$+16.8°(c=4.61, chloroform)	51[j)]	S
10	β-tetralone	1.8	-78	98	$[\alpha]_D^{19}$+18.8°(c=6.31, chloroform)	67[k)]	R
11	$PhCH_2COMe$	1.8	-78	90	$[\alpha]_D^{20}$+17.0°(c=5.76, benzene)	41[l)]	S
12	$c\text{-}C_6H_{11}COMe$	3.9[m)]	-78	90	α_D^{20}+0.182°(l=0.1, neat)	35[n)]	S

a) All reactions were carried out using lithium aluminum hydride partially decomposed by (-)-N-methylephedrine(1 eq) and N-ethylaniline(2 eq) in ether for 3 hr. Spectral(IR and NMR) properties of optically active alcohols were entirely consistent with the assigned structures. b) Calculated on the sample purified by preparative tlc(silica gel, dichloromethane). See the experimental procedure for run 5. c) Measured on the sample obtained by bulb to bulb distillation. See the typical experimental procedures. d) Based on $[\alpha]_D^{21}$-43.1°(c=7.19, cyclopentane). S. Yamaguchi and H.S. Mosher, J. Org. Chem., 38, 1870(1973). e) Calculated on the sample obtained by extractive isolation. See the experimental procedure for run 3. f) Based on $[\alpha]_D$-45.45°(c=5.15, chloroform). R. H. Pickard and J. Kenyon, J. Chem. Soc., 105, 1115(1914). g) Based on $[\alpha]_D^{20}$ -47.7°(c=7, ether). MacLeod, F.J. Welch, and H.S. Mosher, J. Am. Chem. Soc., 82, 876(1960). h) Based on $[\alpha]_D$-45.9°(c=5.15, benzene). J. Kenyon and S.M. Partridge, J. Chem. Soc., 1936, 128. i) Based on $[\alpha]_D^{20}$+34.4°(c=1.97, chloroform). W. Hückel and F. Mössner, Ann., 637, 57(1960). j) Based on $[\alpha]_D^{17}$ +32.7°(c=2.5, chloroform). A.G. Davis and A.M. White, J. Chem. Soc., 1952, 3300. k) Based on $[\alpha]_D$+28.20°(c=7.70, chloroform). R.H. Pickard and W.O. Littlebury, J. Chem. Soc., 89, 1254(1906). l) Based on $[\alpha]_D$+41.82°(c=5.26, benzene). R.H. Rickard and J. Kenyon, J. Chem. Soc., 105, 1115(1914). m) See footnote 12. n) Based on $[\alpha]_D^{20}$+5.68°(neat), d_4^{20} 0.9254. A. Domleo and J. Kenyon, J. Chem. Soc., 128, 1841(1926).

From the experimental detail for run 3, it is evident that, similarly to the asymmetric reduction previously reported,[5] the isolation of optically active alcohol in a pure state and the recovery of (-)-N-methylephedrine and N-ethylaniline can be simply accomplished by a combination of usual extractive workup and distillation. These features would certainly add practical values to the exploited asymmetric reduction.[13]

Having already gained an insight into the stereochemical aspects of asymmetric reaction, we will present the details of the reaction mechanism separately. Further applications of this novel reducing agent to asymmetric reductions of different kinds of achiral ketones are under progress in our laboratory.

References and Notes

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7) Asymmetric reduction of 1 by the reducing agents hitherto reported,[2,3] gave (-)-2 in lower optical and chemical yields. See footnote 13 in ref. 5.

8) S.-s, Jew, S. Terashima, and K. Koga, Chem. Pharm. Bull.(Tokyo), 27, 2351 (1979)., and references cited therein.

9) Detailed examinations on achiral amine additives, N-alkyl substituents of (-)-N-alkylephedrines,[10] reaction solvents, and reaction temperatures were carried out for the reduction of 1. See ref. 5.

10) T. Mashiko, S. Terashima, and S. Yamada, Yakugaku Zasshi, 100, 319(1980).

11) Based on $[\alpha]_D^{20}$-29.5°(c=4.50, methanol). See ref. 10.

12) 3.9 equivalents of the reducing agent was necessary for the complete reduction of cyclohexyl methyl ketone. This might be due to steric hindrance of the cyclohexyl group.

13) Some of the hitherto reported asymmetric reductions[1,2,4] have employed neutral chiral sources and additives for preparing chiral metal hydrides, however, it would take much time to remove them from neutral reaction products efficiently.

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