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ASYMMETRIC REDUCTIONS OF KETONES USING LITHIUM ALUMINIUM HYDRIDE MODIFIED WITH N,N-DIALKYL DERIVATIVES OF (R)-(-)-2-AMINOBUTAN-1-OL

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Abstract : $LiAlH_4$ previously treated with 2 equivalents of (R)-(-)-2-(2-iso-indolinyl) butan-1-ol (a readily available reagent) reduced 2-chloro and 2,4-dimethyl benzophenones into the corresponding benzhydrols with 100% enantiomeric excess. Other examples of ketone reductions are given.

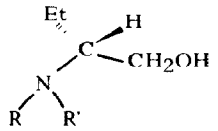
The asymmetric reductions of prochiral ketones with lithium aluminium hydride partially decomposed with various chiral aminoalcohols have been extensively studied in recent years.[1-4] In nearly all cases, these chiral aminoalcohols have two asymmetric centres (as in N-methylephedrine), or even more (as in quinine). Morrison and his coworkers stressed that such reagents are very expensive, the average cost per mole ranging from 350 to over 2600 dollars.[1] Besides, owing to generally constraining operating conditions (low temperatures and high dilutions), such chirally modified aluminium hydrides very often appear to have a limited preparative utility. And finally, chiral modifiers are often easily obtained in only one enantiomeric form, thus preventing control of the chiral sense of the hydride transfer to the ketone.[1]

For all these reasons, we looked for new, and reasonably cheap aminoalcohols, liable to be used for preparing serviceable chiral alkoxyaluminium hydrides. Racemic 2-aminobutan-1-ol (R,S)-**1** is a cheap chemical It can be easily resolved into both its antipodes on the industrial scale.[5,6] And indeed, the enantiomer (R)-(-)-**1** is a by-product of the manufacture of an important antitubercular drug, namely ethanbutol.[6] We first synthesized a variety of new N,N-disubstituted derivatives of (R)-(-)-**1** (which contains only one asymmetric carbon), and we subsequently used them in the asymmetric reduction of acetophenone. Those which gave the best results are described below.

Alkylation of (R)-(-)-**1** with n-butyl bromide in boiling toluene, and in the presence of sodium carbonate, afforded the secondary amine (R)-(-)-**2**.[7] Treatment of the latter with formic acid and acetic anhydride in CH_2Cl_2, followed by reduction of the intermediate formamide with $LiAlH_4$, yielded the tertiary base (R)-(-)-**3**.[7] The aminoalcohols (R)-(-)-**4** and (R)-(-)-**5**[7] were similarly prepared from (R)-(-)-**1**, using benzyl bromide (without Na_2CO_3) in the first step. The pyrrolidine derivative (R)-(-)-**6** was obtained by N-dialkylation of (R)-(-)-**1** with 1,4-dibromobutane.[7,8] The isoindoline (R)-(-)-**7**[7,8] was similarly obtained from (R)-(-)-**1** and α,α'-dichloro-ortho-xylene. 2-Amino-2-phenylethan-1-ol (R)-(-)-**8**[7,9] was N-dialkylated in the same way as above and yielded the bases (R)-(-)-**9** and (R)-(-)-**10**,[7] respectively.

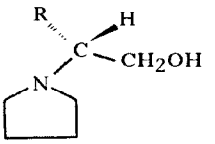
With the above aminoalcohols in hand, the asymmetric reduction of acetophenone was next carried out using $LiAlH_4$ partially decomposed with one, two or three equivalents of aminoalcohol, as shown by the following equation.

$$LiAlH_4 + n\ ROH \longrightarrow LiAl(OR)_nH_{4-n} + n\ H_2 \qquad n = 1,2,3$$

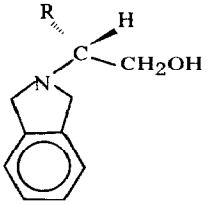


(R)-(-)

1 R = R' = H
2 R = n-Bu ; R' = H
3 R = n-Bu ; R' = Me
4 R = $PhCH_2$, R' = H
5 R = $PhCH_2$; R' = Me



6 R = Et
9 R = Ph



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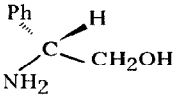

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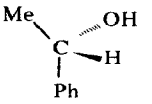
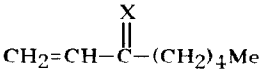
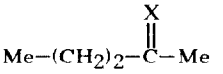


(S)-(-)-**11**



12 X = O
17 X = H,OH



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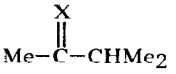
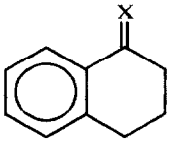


14 X = O
19 X = H,OH



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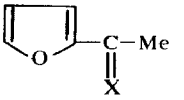
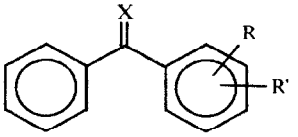
20 X = H,OH



16 X = O
21 X = H,OH



22 X = O
23 X = H,OH

a R = 2-MeO ; R' = H
b R = 2-MeO ; R' = 4-MeO
c R = 2-Me ; R' = 4-Me
d R = 2-Cl ; R' = H
e R = 3-Cl , R' = H
f R = 3-Cl ; R' = 4-Cl

Thus, to an ethereal molar solution of $LiAlH_4$ (6 mmol), a solution of chiral alcohol (1-3 equ.) in Et_2O was added. After stirring at room temperature for 30 min, the mixture was cooled to -15°C, and acetophenone (5 mmol) in Et_2O was added dropwise. After keeping at -15°C for 1h30min, the mixture was acidified and worked up. The (S)-(-)enantiomer of methylphenylcarbinol **11** was obtained in all cases.[7] The results obtained with the aminoalcohols **3** and **5-7** are displayed in Table 1. The enantiomer excess (ee) was determined as the ratio of the specific rotation observed for synthetic (S)-(-)-**11** to that recorded for the optically pure compound. The best results were invariably obtained with $LiAlH_4$ previously treated with two equivalents of chiral aminoalcohol, which implies 2 equ. of the latter and 2 equ. of hydride ion per equ. of acetophenone. The aminoalcohol **7** proved to be the best chiral modifier, the alcohol (S)-(-)-**11** being obtained in 78% yield and with an ee = 63%.

ROH	**3**			**5**			**6**			**7**		
n	1	2	3	1	2	3	1	2	3	1	2	3
ee(%)	8	15	2	2	49	37	9	40	21	7	63	39

Table 1. Enantiomeric excess (ee) of the alcohol (S)-(-)-**11** obtained by reduction of acetophenone with the chiral reagents $LiAl(OR)_nH_{4-n}$

Replacement of the ethyl group in either **6** or **7** by a phenyl group had rather a negative effect on the asymmetric reduction, as it can be seen from Table 2 which summarizes the results obtained with the aminoalcohols **9** and **10**.

ROH	**9**	**10**		
n	2	1	2	3
ee(%)	33	5	44	19

Table 2. Enantiomeric excess of the alcohol (S)-(-)-**11** obtained by reduction of acetophenone with the chiral reagents $LiAl(OR)_nH_{4-n}$ deriving from the aminoalcohols **9** and **10**.

We next studied the asymmetric reduction of various ketones such as **12-16**, using $LiAlH_4$ modified with two equivalents of the aminoalcohol **7** (Table 3). The best results were obtained in the asymmetric reduction of α-tetralone **15** (ee : 41.7%) and 2-acetylfuran **16** (ee : 47%).

Alcohol	**17**	**18**	**19**	**20**	**21**
ee(%)	5.5	17	30	41.7	47

Table 3. Enantiomeric excess of the alcohols **17-21**[7] obtained by reduction of the ketones **12-16** respectively, with the chiral reagent $LiAl(OR)_2H_2$ deriving from the aminoalcohol ROH (**7**).

We finally studied the reduction of various prochiral benzophenones **22a-f**, using as above $LiAlH_4$ previously treated with 2 equ. of the aminoalcohol **7** (Table 4). Thus, reduction of 2-chlorobenzophenone **22d** gave (+)-2-chlorobenzhydrol **23d** in 96% yield, having $[\alpha]_D$ +21.3 (c 0,5, Me_2CO), whereas the literature[10] indicates $[\alpha]_D$ -19 9 (c 0.52, Me_2CO). The phenylurethanne of (+)-**23d** had m.p. 120°C and $[\alpha]_D$ -43 (c 0.5, Me_2CO), and these values remained unchanged after further recrystallization. Similarly, asymmetric reduction of 2,4-dimethylbenzophenone **22c** afforded the corresponding benzhydrol (+)-**23c**[7] with more than 95% ee, as shown by the ^1H NMR spectrum taken in the presence of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphoratoleuropium III.

The 2-methoxy substituted benzophenones **22a,b** led to markedly lower optical yields. The ee was negligible in the case of the 3-chlorobenzophenones **22e,f**. All the benzhydrols thus obtained were dextrorotary.[11]

Benzhydrol **23**	R	R'	ee (%)
a	2-MeO	H	66
b	2-MeO	4-MeO	34
c	2-Me	4-Me	>95
d	2-Cl	H	100
e	3-Cl	H	~3
f	3-Cl	4-Cl	~8

Table 4. Enantiomeric excess of the benzhydrols **23a-f**, obtained by reduction of the ketones **22a-f** with the chiral reagent $LiAl(OR)_2H_2$ deriving from the aminoalcohol ROH (**7**).

Conclusion

It is very often assumed that asymmetric reduction of prochiral ketones is best achieved when the carbonyl carries a "large" and a "small" substituent, as exemplified with acetophenone which has been the object of numerous studies of this kind. However, the present work shows that good results can be obtained when the carbonyl carries two large groups, as exemplified with 2-chlorobenzophenone **22d**. Since the chiral aminoalcohol (R)-(-)-**7** is readily available, and comparatively cheap, the above syntheses of the optically pure benzhydrols (+)-**23c** and (+)-**23d** appear to have both an economical and preparative value. Since **7** can be obtained in both enantiomeric forms, this also applies to the above benzhydrols. Apart from some natural compounds, such as menthol, very few alcohols can be obtained in optically active form. For this reason, the benzhydrols (+)-**23c,d** may prove useful chiral intermediates in asymmetric synthesis.

References and notes

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7. Yields and physical constants of the optically pure compounds : **2**, 83%, b.p. 103°C/12 mm, $[\alpha]_D$ -29 (c 5, MeOH) ; **3**, 75%, b.p. 98°C/12 mm, $[\alpha]_D$ -4 (c 5, MeOH) ; **4**, 87.5%, m.p. 70-72°C, $[\alpha]_D$ -22.5 (c 5, MeOH) ; **5**, 78%, b.p. 96°C/0.03 mm, $[\alpha]_D$ -2 (c 2, MeOH) ; **6**, 73.5%, oil, $[\alpha]_D$ -49.5 (c 8, PhMe) ; **7**, 60%, m.p. 57-58°C, $[\alpha]_D$ -20 (c 1, EtOH) ; **8**, m.p. 73°C, $[\alpha]_D$ -27 (c 5, MeOH) ; **9**, 65%, m.p. 58°C, $[\alpha]_D$ -36 (c 1, MeOH) ; **10**, 23%, m.p. 78°C, $[\alpha]_D$ -20.5 (c 5, MeOH) ; **11**, $[\alpha]_D$ -45.5 (c 5, MeOH) ; **17**, $[\alpha]_D$ +16.9 (neat) ; **18**, $[\alpha]_D$ +13.72 (neat) ; **19**, $[\alpha]_D$ +4.85 (neat) ; **20**, $[\alpha]_D$ +32.7 (c 10.7, $CHCl_3$) ; **21**, $[\alpha]_D$ +20.8 (c 1.27, $CHCl_3$) ; **23a**, $[\alpha]_D$ -68.1 (c 0.67, THF) ; **23b**, $[\alpha]_D$ -70 (c 0.8, Me_2CO) ; **23d**, $[\alpha]_D$ -19.9 (c 0.5, Me_2CO) , **23e**, $[\alpha]_D$ +30.3 (c 1.1, Me_2CO).
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