# Asymmetric Synthesis. Part 6.[1] Asymmetric Reduction of Aminoketones with (−)-Bornan-2-*exo*-yloxyaluminium Dichloride

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α-Dialkylaminoacetophenones and β-dialkylaminopropiophenones have been reduced asymmetrically with (−)-bornan-2-*exo*-yloxyaluminium dichloride to the corresponding aminoalcohols in 58—92% enantiomeric excess. The absolute configurations of the predominant enantiomers, (*S*) and (*R*) for α- and β-series respectively, follow from six-membered cyclic transition states. Three acetylpyridines have been similarly reduced, but with much less enantioselectivity (12—37%).

During the past few years, we have employed a number of chiral alkoxyaluminium dichlorides, especially the one, (1), derived from (−)-bornan-2-*exo*-ol (isoborneol), for asymmetric reduction of ketones [1,2] and aldehydes [3] with varying degrees of enantioselectivity. One major problem with these reductions is the isolation and purification of the products which require either preparative g.l.c.[3] or controlled steam distillation [4] (see, however, ref. 5). The use of aminoketones as substrates gives no separation problem, however, the resulting aminoalcohols being soluble in acids. Moreover, the presence of nitrogen may enhance the asymmetric induction, as has indeed been observed in the reduction of the ketones (5)—(7) with lithium aluminium hydride modified by (−)-menthol.[6] Some of the aminoalcohols are physiologically active and their preparation in optically pure form is highly desirable. With these considerations in view, we attempted to reduce the aminoketones (2)—(10) asymmetrically with (−)-bornan-2-*exo*-yloxyaluminium dichloride (1) which is the most reactive reagent of this group.[7] Russian workers [8] have recently reduced some of these aminoketones with chiral organomagnesium compounds with optical yields of 65—70% (in two cases) but the chemical yields were extremely poor (3—38%). The reduction of the three Mannich bases (5)—(7) by the Italian workers [6] was accompanied by 58—73% asymmetric induction and is simpler from the operational point of view.

## Results and Discussion

The reduction of the ketones (2)—(10) was carried out with a ten-fold excess of the reagent (1) † in ether–tetrahydrofuran at 0 °C and was almost complete (*ca.* 95%). The absolute rotations of the aminoalcohols derived from ketones (2),[9] (5)—(7),[6] and (8)—(10) [10] are known and the enantiomeric purity was determined from their specific rotations. The remaining two alcohols from ketones (3) and (4) were converted into esters of (+)-*O*-methyl-mandelic (-phenylglycolic) acid and the enantiomeric excess in each case was determined by measuring the diastereoisomeric ratio from the peak intensities of $OCH_3$ and HC-OMe in the $^1$H n.m.r. spectrum.[11] The signal positions and the differences in chemical shifts of these protons (see Experimental section) corresponded closely to those reported for the higher homologues.[6] The absolute configurations of the 2-dialkylamino-1-phenylethanols (12) [8] and 3-dialkylamino-1-phenylpropanols (13) [6] are well-established. In the present reduction, the predominant enantiomers of all six aminoethanols and aminopropanols are dextrorotatory (entries 1—6) and are structurally related, having (*S*) and (*R*) configurations respectively, the difference in configurational notation being due to the sequence rule. Evidently, the structurally similar ketones (2)—(7) lead to analogous topographical features in the diastereoisomeric activated complexes and the configuration follows from the preferred six-membered cyclic transition state (11) in which the crowded C-1 of the bornane nucleus and the bulky phenyl group in the ketones are oppositely oriented.[2] This may be construed as additional evidence for the configurational assignment.

Attempts to resolve the (±)-aminoalcohols from ketones (3) and (4) with (−)-dibenzoyltartaric acid [9] were unsuccessful, giving only partially resolved alcohols of low optical purity (9 ± 3%); this was shown by their $^1$H n.m.r. spectra, using chiral shift reagent,‡ and from the $^1$H, $^{13}$C, and $^{19}$F n.m.r. spectra ‡ of the derived esters with (*S*)-(−)-α-methoxy-α-trifluoromethyl-α-phenylacetic acid.[12]

An inspection of the data in the Table shows that the enantioselectivity in the reduction of the aminoketones (2)—(7) is moderate to high (58—92%) (lowest for the piperidine derivatives and highest for the morpholine compounds) and compares favourably with that reported by both Russian and Italian workers. The easy accessibility of the reagent (1), the predictability of the product configuration from a simple transition state model, and the high chemical and optical yields make the method a practical one. The small ketonic impurity (5—7%) could be removed by fresh reduction of the product with lithium aluminium hydride. The average asymmetric induction in the reduction of dialkylaminoacetophenones is *ca.* 66% which exactly coincides with that for the reduction of the structurally similar isobutyl phenyl ketone (66%) [2] using the same reagent. The effect of nitrogen in the substrates is thus non-existent. The very high asymmetric induction (92%) in the reduction of β-morpholinopropiophenone (7), the highest ever achieved with the present reagent, may be linked with the extra oxygen in the molecule through some obscure mechanism. The stereoselectivity, however, considerably decreased (71%) in the reduction of the lower homologue (4). The three acetylpyridines (8)—(10) were reduced to 1-(2-, 3-, and 4-pyridyl)ethanols, but the enantioselectivity was low, the highest being 37% for 3-acetylpyridine (9). They all showed an excess of the dextrorotatory (*R*)-enantiomer [11] in accordance with the transition state (11).

We also reduced the three α-dialkylaminoacetophenones (2)—(4) with lithium aluminium hydride partially decomposed with (−)-menthol (3 mol) under the optimum conditions specified by the Italian workers.[6] The enantiomeric purity of the aminoalcohols, obtained quantitatively, was found to

† The reagent was prepared from a mixture of *exo*- and *endo*-bornan-2-ols (9 : 1) obtained directly from the reduction of (+)-camphor with lithium aluminium hydride.

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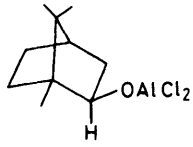


(1)

$PhCO[CH_2]_nNR_2$

(2) $n = 1$, $NR_2 = NMe_2$

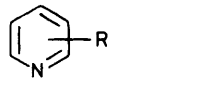
(3) $n = 1$, $NR_2$ = N⬡

(4) $n = 1$, $NR_2$ = N⬡O

(5) $n = 2$, $NR_2 = NMe_2$

(6) $n = 2$, $NR_2$ = N⬡

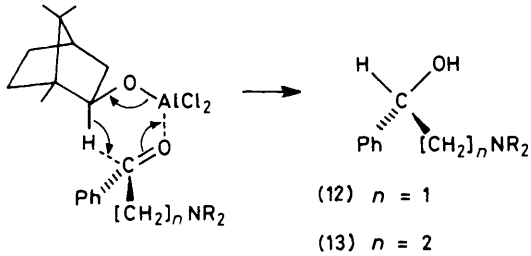
(7) $n = 2$, $NR_2$ = N⬡O



(8) R = 2-COMe

(9) R = 3-COMe

(10) R = 4-COMe



(11)

(12) $n = 1$

(13) $n = 2$

be very poor (15.5, 12.5, and 12.0% respectively) showing that the reagent does not work well for all aminoketones.

## Experimental

M.p.s are uncorrected. $^1H$ N.m.r. spectra were recorded on a Varian EM-390 90-MHz spectrometer for solutions in $CDCl_3$ with $Me_4Si$ as internal standard; the two spectra for the determination of the diastereoisomeric ratio by Raban–Mislow's method were taken with a JEOL 100-MHz machine for solutions in $CDCl_3$. Specific rotations were measured for solutions in methanol (*c*, 8—10%) on a Perkin-Elmer model 241 polarimeter and i.r. spectra on a Perkin-Elmer model 237B spectrophotometer. (+)-Mandelic acid (99% purity) and (+)-bornan-2-one (camphor) were supplied by Aldrich Chemical Co., U.S.A. Organic extracts were dried over anhydrous $Na_2SO_4$; light petroleum refers to the fraction with b.p. 60—80 °C, and ether refers to diethyl ether.

*α-Dialkylaminoacetophenones* (2)—(4).—α-Dialkylaminoacetophenones were prepared following a published procedure [13] by condensation of phenacyl bromide with dimethylamine, piperidine, and morpholine, respectively, in anhydrous ether and were purified by distillation. Their spectral data are as follows. α-Dimethylaminoacetophenone (2); δ 8.00 (2 H, dd, *J* 8 and 2 Hz, ArH), 7.48 (3 H, m, ArH), 3.69 (2 H, s, $COCH_2N$), and 2.20 (6 H, s, $NMe_2$). α-Piperidinoacetophenone (3); [14] δ 8.00 (2 H, dd, *J* 8 and 2 Hz, ArH), 7.45 (3 H, m, ArH), 3.70 (2 H, s, $COCH_2N$), 2.50 (4 H, t, *J* 6 Hz, ring $NCH_2$), and 1.51 (6 H, m, 3 × $CH_2$). α-Morpholinoacetophenone (4); [14] δ 7.96 (2 H, dd, *J* 8 and 2 Hz, ArH), 7.42 (3 H, m, ArH), 3.60 (6 H, m, $COCH_2N$ + 2 × $OCH_2$), and 2.50 (4 H, t, *J* 6 Hz, 2 × $NCH_2$). All the three ketones had $\nu_{max.}$ 1 690 $cm^{-1}$ ($CHCl_3$).

**Table.** Asymmetric reduction of aminoketones with (−)-bornan-2-*exo*-yloxyaluminium dichloride (1) [a]

| Entry | Amino-ketone | Yield of alcohol (%) | $\alpha_D^{25}$ (°) [b] | Enantiomeric excess (%) | Configuration |
|---|---|---|---|---|---|
| 1 | (2) | 78.0 | +28.1 [c] | 66.7 | (+)-(*S*) |
| 2 | (3) | 90.5 | +28.9 | 60.0 [d] | (+)-(*S*) |
| 3 | (4) | 81.5 | +33.3 | 71.0 [d] | (+)-(*S*) |
| 4 | (5) | 82.0 | +18.4 [e] | 65.0 | (+)-(*R*) |
| 5 | (6) | 84.5 | +17.0 [e] | 58.0 | (+)-(*R*) |
| 6 | (7) | 75.5 | +10.5 [e] | 92.0 | (+)-(*R*) |
| 7 | (8) | 75.0 | +6.5 [f] | 11.5 | (+)-(*R*) |
| 8 | (9) | 60.0 | +20.9 [f] | 37.0 | (+)-(*R*) |
| 9 | (10) | 70.5 | +5.8 [f] | 14.7 | (+)-(*R*) |

[a] A mixture of *exo*- and *endo*-bornan-2-ols (9 : 1) was used. [b] Corrected for ketonic impurities (5—7%) as determined by $^1H$ n.m.r. [c] Maximum value [9] of $\alpha_D$, 42.1°. [d] Determined by Raban–Mislow's method.[11] [e] Maximum values [6] of $\alpha_D$, 28.2°, 29.3°, and 11.4° for 3-dimethylamino-, 3-piperidino-, and 3-morpholino-1-phenylpropanols, respectively. [f] Maximum values [10] of $\alpha_D$, 56.6°, 56.4°, and 39.5° for 2-, 3-, and 4-pyridylethanols, respectively.

(±)-2-*Dialkylamino*-1-*phenylethanols* (12).—The racemic aminoethanols were prepared by reduction of the aminoketones (2)—(4) with lithium aluminium hydride and characterised as follows. (±)-2-Dimethylamino-1-phenylethanol [9] (12; $NR_2 = NMe_2$); δ 7.20 (5 H, m, ArH), 5.95 (1 H, s, OH), 4.65 (1 H, dd, *J* 8 and 8.5 Hz, α-H), 2.35 (2 H, m, 2-$H_2$), and 2.30 (6 H, s, $NMe_2$). (±)-2-Piperidino-1-phenylethanol (12; $NR_2$ = piperidino), m.p. 71—72 °C (light petroleum) (Found: C, 76.0; 9.3; N, 6.3. $C_{13}H_{19}NO$ requires C, 76.1; H, 9.3; N, 6.8%); δ 7.30 (5 H, m, ArH), 4.66 (1 H, dd, *J* 7 and 7.5 Hz, α-H), 3.80 (1 H, s, OH), 2.60 (2 H, m, 2-$H_2$), 2.40 (4 H, m, ring 2 × $NCH_2$), and 1.50 (6 H, m, 3 × $CH_2$). (±)-2-Morpholino-1-phenylethanol (12; $NR_2$ = morpholino), m.p. 83—84 °C (light petroleum) (Found: C, 69.1; H, 8.5; N, 6.7. $C_{12}H_{17}NO_2$ requires C, 69.5; H, 8.2; N, 6.7%); δ 7.28 (5 H, m, ArH), 4.66 (1 H, dd, *J* 8 and 8.5 Hz, α-H), 4.50 (1 H, s, OH), 3.65 (4 H, m, 2 × $OCH_2$), 2.60 (2 H, m, 2-$H_2$), and 2.40 (4 H, m, ring 2 × $NCH_2$).

β-*Dialkylaminopropiophenones* (5)—(7) *and the Corresponding Aminopropan*-1-*ols* (13).—The Mannich bases were prepared in the usual way [15] and were reduced to the racemic aminoalcohols which have already been discussed by Andrisano *et al.*[6]

*Acetylpyridines* (8)—(10).—The 2-, 3-, and 4-acetylpyridines were prepared [10] from the respective pyridinecarboxylic acids by esterification, condensation of the esters with ethyl acetate, and subsequent hydrolysis.

*Reduction Procedures.*—All reductions were carried out in duplicate or triplicate by the following procedure. A mixture of (−)-bornan-2-*exo*-ol (90%) and (+)-bornan-2-*endo*-ol (10%), obtained by reduction of (+)-bornan-2-one with lithium aluminium hydride,[1] was used instead of pure (−)-bornan-2-*exo*-ol. Lithium aluminium hydride solution in *ca.* 1M-ether was prepared and standardised.[16]

To an ice-cold solution of anhydrous aluminium chloride (3.2 g, 24 mmol) in ether (20 ml), was added a 1M-ethereal solution of lithium aluminium hydride (7 ml, 7 mmol) followed by (−)-bornan-2-*exo*-ol (4.3 g, 28 mmol) in ether

(25 ml) with stirring. The reaction vessel was taken out of the ice-bath and stirring was continued until the temperature rose to 10 °C. The solution was again cooled to 0 °C and a solution of the aminoketone (2.8 mmol) in ether (5 ml) was added dropwise with vigorous stirring. Turbidity occurred and was removed by addition of dry tetrahydrofuran (25—30 ml), and the mixture was stirred for a further 5 h at 0 °C. After the reaction mixture had been stirred overnight at room temperature, it was decomposed with cold 1M-sulphuric acid. The organic layer was separated, the aqueous layer extracted with ether (3 × 25 ml), and the acidic solution was carefully basified with aqueous 10% sodium hydroxide. The liberated aminoalcohol was taken up in ether, the ethereal layer dried, and the solvent removed under reduced pressure. The crude product was directly used for measurement of optical rotation and $^1$H n.m.r. The amount of aminoketone (5—7%) was determined from the signal (m) at δ 8.00 due to the two aromatic H's *ortho* to the carbonyl group. In some experiments, the products were sublimed at reduced pressure but the optical rotation did not change to any appreciable extent.

In the case of the pyridyl ketones, the recovery was relatively low because of the higher solubility of the resultant alcohols in water.

For the determination of the enantiomeric excess of partially resolved alcohols from the ketones (3) and (4) (*vide supra*), tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium was used as the chiral lanthanide shift reagent.

*Formation of Diastereoisomeric Esters of the Alcohols* (12; $NR_2$ = *piperidino*) *and* (12; $NR_2$ = *morpholino*).—In a dry test tube equipped with a rubber septum, the reagents were injected in the following order: dry pyridine (3 ml), (+)-*O*-methylmandeloyl chloride (277 mg, 1.5 mmol), carbon tetrachloride (3 ml), and the aminoalcohol (1 mmol). The mixture was shaken and allowed to stand until there was no more formation of crystalline pyridine hydrochloride. The product was worked up in the usual way and the ester was isolated in 88—90% yield. Both the esters gave expected $^1$H n.m.r. spectra. The piperidino derivative had the α-H and OMe signals of HCOMe at δ 4.838 and 4.774 (Δν 6 Hz) and 3.412 and 3.384 (Δν 2.7 Hz), respectively, while the morpholino derivative showed these signals at δ 4.828 and 4.779 (Δν 5 Hz) and 3.392 and 3.363 (Δν 2.9 Hz). The major diastereoisomers in both compounds had the signals situated at higher field.

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