A Novel Chiral Auxiliary from Chiral Spiranes. *cis,cis*-(+)- and (−)-Spiro[4.4]nonane-1,6-diol as Chiral Modifier in Lithium Aluminium Hydride Reduction of Phenyl Alkyl Ketones†

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$LiAlH_4$ reduction of phenyl alkyl ketones employing the hitherto unexplored chiral auxiliary *cis,cis*-(+)- and (−)-spiro[4.4]nonane-1,6-diol as chiral modifier gives the corresponding alcohol in 85–90% e.e. (enantiomeric excess).

The development of methodologies to effect chiral syntheses efficiently, economically and in high enantiomeric purity is of vital importance because of the emergence of a number of chiral drugs.[1] A large number of chiral auxiliaries both from natural and synthetic origin have been prepared[2] and studied but no report pertaining to the application of chiral auxiliaries from inherently dissymmetric chiral spiranes is available to date.

The molecular models reveal that the enantiomers of *cis,cis*-spiro(4.4)nonan-1,6-diol **1** possess the conformational rigidity as well as molecular dissymmetry necessary for effective diastereofacial selectivity. Accordingly, *cis,cis*-(+)- and *cis,cis*-(−)-spiro[4.4]nonane-1,6-diol **1** were prepared by Cram's procedure[3] and resolved *via* camphenates.[4]

We report here the reduction of phenyl alkyl ketones **2** employing **1** as chiral lithium aluminium hydride (LAH) modifiers.

The experimental procedure involved the addition of *cis,cis*-(+)-**1** (10 mmol) to a well stirred solution of LAH (0.4 mol dm^{-3}, 10 mmol) in diethyl ether at 0 °C under a nitrogen atmosphere and stirred for 2 h at the same temperature. Absolute ethanol (10 mmol) in dry diethyl ether (5 ml) was added slowly and stirred for 1 h. The LAH complex thus formed was chilled to the desired temperature, dry phenyl alkyl ketone **2** (5 mmol) was added slowly and stirred for 20–24 h. The reaction mixture was quenched by the addition of HCl (2 mol dm^{-3}, 5 ml) at −20 °C. Extractive workup with hexane followed by vacuum distillation afforded corresponding (+)-

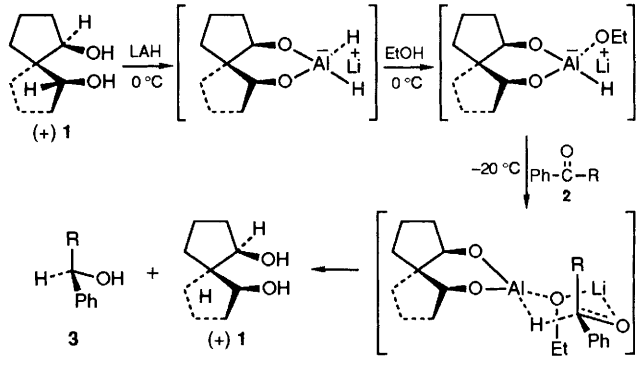

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Table 1

Entry	Substrate **2** R/mmol	**1**/mmol	LAH/mmol	Temp./°C	Yield (%)	$[\alpha]_D^{25}$ of **3**	E.e.(%)
1	Me,5	(+),10	10	−80	80	+39.0	98
2	Me,5	(+),10	10	−60	77	+38.4	96
3	Me,5	(+),10	10	−40	76	+36.0	90
4	Me,5	(+),10	10	−20	75	+35.8	89
5	Me,5	(+),10	10	0	75	+30.0	70
6	Et,5	(+),10	10	−20	70	+29.0	90
7	Pr,5	(+),10	10	−20	65	+45.0	90
8	Bu^t,5	(+),10	10	−20	69	+14.45	85
9	Et,5	(−),10	10	−20	62	−28.0	87
10	Pr,5	(−),10	10	−20	65	−40.2	85

phenyl alkyl alcohol **3** in 70–75% yield. The e.e. were determined by ^{1}H NMR of (+)-α-methoxy-α-[(trifluoromethyl)phenyl]acetic esters.[5] *cis,cis*-(+) **1** was recovered in 90% yield from the aqueous portion without any loss of optical purity. We have studied the reduction of various phenyl alkyl ketones **2** following the above reduction procedure. The results are summarized in Table 1.

The entries 1–4 depict that enantioselectivity decreases from 98 to 90% as the temperature is raised from −80 to −40 °C as expected and then remains nearly constant from −40 to −20 °C.

This behaviour is slightly inconsistent with the literature reports[6–8] wherein the enantioselectivities in the chiral-LAH reduction of phenyl alkyl ketones have been found to decrease continuously with increase in reaction temperature, *viz.* in the LAH-reduction of acetophenone **2** (R = Me), employing chiral binaphthol as chiral modifier the enantiomeric excesses, 95% at −100 to −78 °C; 90% at −78 °C; 84% at −50 °C and 77% at −20 °C, respectively, have been reported.[7c]

High e.e.s at low temperature are obvious because non-bonded interactions, which provide highly organized diastereoisomeric transition states, can play their role effectively. As the temperature is raised, these non-bonded interactions weaken and the diastereoisomeric organized structure begins to collapse, resulting in the decrease in e.e.

The low temperature effects are nearly the same as those observed with chiral spirocyclic auxiliary **1**. However, as the temperature is raised, it is probably that the inherent conformational rigidity still restricts the transition state mobility and inherent dissymmetry continues to play its role, although to a somewhat lesser extent.

The stereochemical course of this chiral reduction seems to be in agreement with diastereoisomeric six-membered cyclic stereocorrelation model **4**.[7] The present studies indicate that the chiral spirocyclic auxiliary **1** with more steric bulk can potentiate high enantioselective reduction and possibly at a much more convenient working temperature.

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