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ASYMMETRIC REDUCTION OF KETONES USING $LiAlH_4$ MODIFIED WITH CHIRAL 1,2-AMINODIOLS

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Summary: Four chiral aminodiols from ring opening of (S)-propylene oxide and ethylene oxide with n-butylamine and (R) or (S)-α-methylbenzylamine were used to modify $LiAlH_4$. Asymmetric reduction of acetophenone and propiophenone gave the highest percent enantiomeric excess when the modifer was made from (S)-oxide and (S)-amine.

There have been a number of studies of asymmetric reduction using $LiAlH_4$ modified with chiral carbinolamines. Typically, the chiral modifiers have contained a 2° or 3° carbinol group and a 3° amine group with the NR_2 and OH in a 1,2 or 1,3 relationship to each other. Some modifiers have been natural products[1], others simple derivatives of natural products[2] or compounds having another primary use[3], whose structures appeared to provide a suitable positioning of appropriate functionalities and chiral centers. Such modifiers have been used rather successfully in some instances, but they provide relatively little information about the essential structural and stereochemical characteristics required in an effective modifier.

Recently there have been a few attempts to construct carbinolamine modifiers that have particular structural and stereochemical features[4]. Notable examples are the 1,3-carbinolamines synthesized by Cohen and coworkers[4a]. Even the simple modifier 1 was capable of substantial asymmetric induction when added to $LiAlH_4$ solutions prior to the reduction of acetylenic ketones (34, 36 and 72% ee) and acetophenone (60% ee).

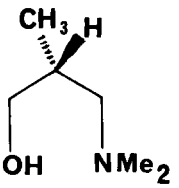
We have been investigating some synthetic carbinolamine modifiers of a type that has not been studied previously[5]. These new modifiers are aminodiols having a 3° amine nitrogen, two of whose ligands bear chiral carbinol centers in a 1,2 relationship to the nitrogen. The stereoformulas for four of these modifiers are shown in drawings 2-5. They were synthesized by the reaction of an appropriate 1° amine with two equivalents of (S)-propylene oxide[6] (2,4,5) or ethylene oxide (3).

Reductions of acetophenone and propiophenone were carried out using the general procedure of Cohen[4a]. Reductions were quantitative. The chiral carbinolamine modifiers could be

extracted quantitatively from reaction mixtures (with dilute acid) and recycled. Pure alcohol reduction products were obtained by distillation; the % ee values were the same before and after preparative gas chromatography.

By systematic structural and stereochemical engineering we were able to show how the carbinol chiral centers and the chiral carbon center next to nitrogen contribute to the overall asymmetric induction (Table 1). With just carbinol chirality (S,S-2) R alcohols are produced with respectable % ee. Using a similar modifier with no carbinol chirality, but an (R)-α-methylbenzyl group next to nitrogen (R-3), alcohols with an S configuration and low % ee result. Both chiral directing influences are expressed in the epimeric modifiers 4 and 5. In 4 the stronger R-directing induction of the S,S carbinol groups is opposed by the weaker S-directing (R)-α-methylbenzyl unit, resulting in R alcohols of only fair % ee. In 5, however, the (S)-α-methylbenzyl unit and the S,S carbinol centers both work to produce R configurations and the % ee is quite substantial. In fact it is among the highest that has been observed with carbinolamine systems for the usual test ketones, acetophenone and propiophenone.

The role of the 3° amine and carbinol functions deserves further comment. It is clear that alkoxy groups are introduced at Al via reaction with the carbinol OH. There has been some speculation that the 3° amine function participates via coordination of its nitrogen with Al. It seems more likely, however, that it coordinates Li^+ which is also coordinated to the carbonyl oxygen, activating it for hydride acceptance[7]. Thus the bifunctional carbinolamine modifiers can be considered to be chiral bridges (alkoxy bound to Al and N-coordinated to Li^+) in an ensemble encompassing both atoms of the carbonyl group. The two facets of the modification possible with a carbinolamine can act unilaterally to induce asymmetric reduction, i.e., the use of chiral tertiary amines alone[8] or chiral carbinols alone[9,10] is sufficient. Such modifiers are generally inferior[11] to carbinolamines in terms of % ee. Disproportionation to produce $LiAlH_4$ occurs with some carbinol modifiers[10e] ($2LiAlH_2(OR^*)_2 \rightarrow LiAl(OR^*)_4 + LiAlH_4$). Carbinolamines could function as effective chiral modifiers even if $LiAlH_4$ is the hydride species responsible for reduction. One of the tertiary nitrogens of a chiral tetraalkoxyaluminum species from disproportionation might coordinate with Li^+ and thus attract AlH_4^- to a chiral environment. Thus even if there is some disproportionation in a carbinolamine-modified system the $LiAlH_4$ might function as a chiral reducing agent. However, it would not necessarily yield the same configuration of products as other reducing species.



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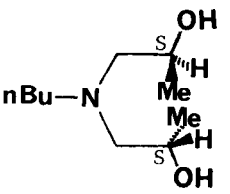

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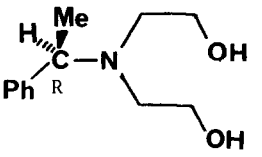

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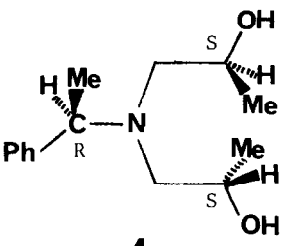

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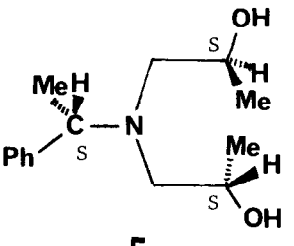

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TABLE 1

Modifier	Ketone	Isolated Yield of Alcohol (%)	%ee(Config.) of Alcohol	Remarks
2	A	85	44(R)	Induction by carbinol centers
2	P	85	57(R)	
3	A	87	10(S)	Induction by chiral center next to N
3	P	97	10(S)	
4	A	90	35(R)	Carbinol center induction opposed by that of chiral center next to N
4	P	88	19(R)	
5	A	98	82(R)	Carbinol induction reinforced by that of chiral carbon next to N
5	P	98	77(R)	

A=acetophenone P=propiophenone

Synthetic modifiers can give high %ee and they allow for manipulation of structure and stereochemistry in systematic ways. The flexibility of our aminodiol system is a good example. We are exploring other substrates, comodifiers and modifiers from other chiral epoxides and amines in vigorous pursuit of even higher %ee values.

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11. See Ref. 10a for a notable exception.

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