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Thiol and Disulfide Derivatives of Ephedra Alkaloids 2: A Mechanistic Study of Their Effect on the Addition of Diethyl Zinc to Benzaldehyde

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Abstract: Thiol and disulfide derivatives of ephedrine have been shown previously to catalyse in high enantiomeric excess (ee) the reaction of diethyl zinc with benzaldehyde. We find that this reaction involves non-linear correlations between the ee of product and catalyst. Osmotic measurements indicate a high degree of aggregation of the zinc thiolates. The behaviour of the thiol derivatives deviates sharply from that of the oxygen analogue, N-methyl ephedrine.

Many of the principles for the design of ligands for metal catalysed enantioselective synthesis[1] have come from the study of the addition of diethyl zinc to aldehydes. To date β-amino alcohols such as (-)-3-exo-(dimethylamino)isoborneol (DAIB) 1[2] and N-alkylated derivatives of ephedrine[3] 3 have played a central role in this reaction (**Scheme 1**).
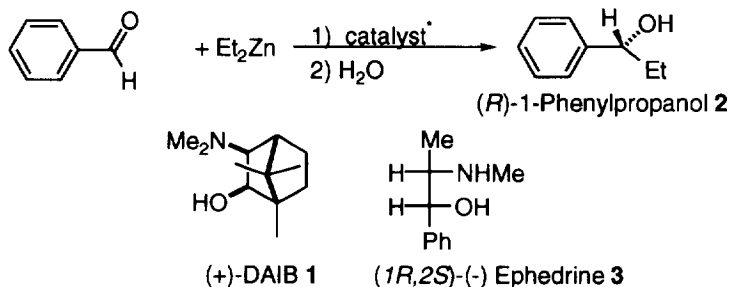
Scheme 1

We reported [4] recently that β-amino thiol derivatives N-methyl ephedrine disulfide 5 (NMED) and N-methyl ephedrine thiol in the form of its more stable HCl salt 6 (NMET.HCl), both derived from N-methyl ephedrine 4 (NME), give excellent ee's in this reaction.[5] Kang *et al* subsequently reported even better results with analogue 7, which is claimed to be stable as the free thiol (**Figure 1**)[6].
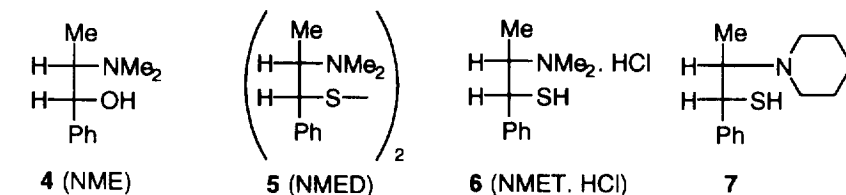

Figure 1

Previous investigations on β-amino alcohols such as **1**[7] have demonstrated pronounced non-linear effects[8], which have proved to be diagnostic for understanding of the mechanistic pathway. To this end determinations of the ee of product (major enantiomer in all cases have *R* absolute configuration) as a function of ee of catalyst using ligands **4**, **5** and **6** were carried out (**Graph 1**). As far as we are aware this is the first time (surprisingly) that NME **4** has been examined.
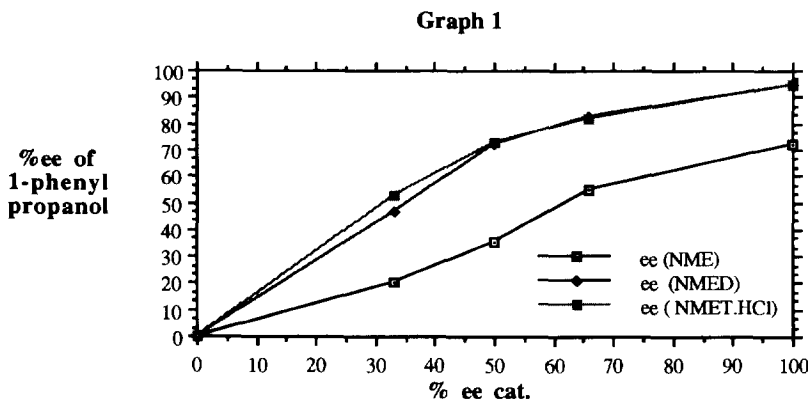
Graph 1

All points in Graph 1 have been determined in duplicate and the errors are ± 2%. For (NME) **4** the relationship is essentially linear but for both (NMED) **5** and (NMET.HCl) **6** pronounced positive non-linear effects are observed .

The following step in the unravelling of the mechanistic aspects is elucidation of how NMED **5** is activated. Clearly the disulfide linkage must be reduced in some fashion. An initial hypothesis[5] was that the diethyl zinc acts as a source of hydride *via* β-hydride transfer; the small amount of benzyl alcohol (<1%) always found suggests that such chemistry is possible (**Scheme 2**).
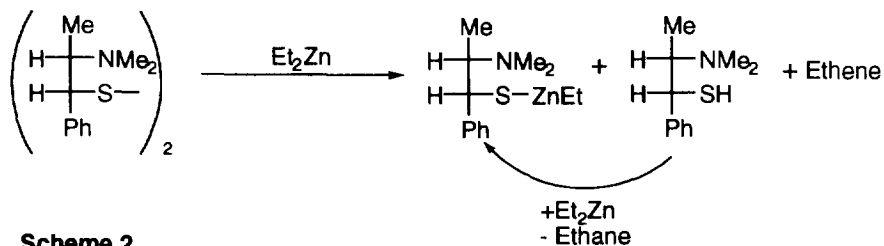
Scheme 2

Analysis of the gas evolved (Toppler pump) in the reaction showed both ethene and ethane to be present as a 1:9 ratio, but the gas evolved was only approximately 5% of the theoretical amount. Addition of benzaldehyde to the reaction mixture to mimic more closely the actual reaction conditions did not lead to an increase in the amount of gas evolved. These results strongly suggest that, although β hydride transfer occurs, this is only a minor mechanistic pathway. We suggest on the basis of these results that alkylation of the disulfide moiety occurs to generate thioether and thiolate, the latter of which is the active catalyst in this reaction (**Scheme 3**). Note that slightly higher ee's of product are consistently obtained using the disulfide **5** compared with thiol **6** (as the HCl salt). This may be due to the presence of chloride ions, which are reported

to lower enantioselection in analogous asymmetric Grignard reactions [9].
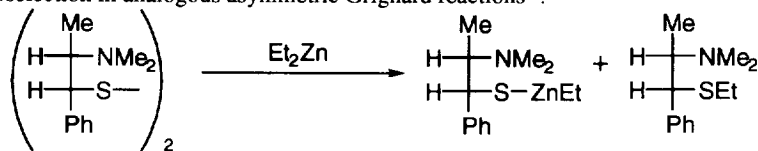
Scheme 3

As a clean stoichiometric relationship is not involved with **5** studies of aggregation phenomena were carried out with HCl salt **6**. A cryoscopic molecular mass method was used to determine the extent of aggregation in benzene using enantiomerically pure **4** and **6** with different concentrations of diethyl zinc (**Table 1**).

Table 1

Et$_2$Zn (equiv.)	Ligand Type (1 equiv.)	Expected Mol. Mass	Mol.Mass Determined	oligomeric structure
1	4	274	770	dimer / tetramer (1:1)
2	4	397	425	monomer
1	6	290	1215	tetramer
2	6	413	364	monomer

Errors in molecular mass determination are no more than ±2%. There is clearly a dramatic difference in the behaviour of amino alcohol **4** and amino thiol **6**. With a single equivalent of diethyl zinc **4** is heavily aggregated. On the assumption that only monomer , dimer and tetramer (no trimer) are involved the aggregate must be more than 50% tetramer. The aggregation is completely broken up by an additional equivalent of diethyl zinc; we assume on the basis of precedent[7] that the monomeric ligand-ethylzinc complex associates with an extra equivalent of diethylzinc. In view of the fact that non-linear effects are not found with **4** one may conclude that the equilibria between the dimeric and tetrameric aggregates, including heterochiral combinations in the case of optically impure **4**, are rapid compared with the rate of reaction.

The curves observed in Graph 1 for **5** and **6** are consistent with the mathematical models developed recently by Kagan *et al.* [10] for dimeric aggregation. However, with a single equivalent of diethyl zinc **6** clearly forms the tetramer. The greater tendency to form higher order aggregates for the sulfur containing system may be rationalised on the basis of the enhanced polarisibility of the sulfur atom coupled with the reduced tendency of the zinc thiolate to diminish the Lewis acidity of the zinc centre. The effect of extra diethyl zinc is dramatic - the homochiral aggregates appear to be broken up entirely. To achieve the non-linear effects that we have observed one must assume that the heterochiral (meso) aggregates are stable to extra diethyl zinc and thus an aggregation induced deracemisation process can occur.

Experimental:
Non-linear effect determination:

To a solution of 1 mmol of catalyst in dry toluene (10 mL) was added 4 mL of a 1M diethyl zinc solution in hexane under an argon atmosphere. After stirring for 2h the mixture was cooled to -20°C and 0.3 mL benzaldehyde (20 mmol) was added. The solution was stirred at room temperature and aliquots (0.3mL)

taken filtered over silica with 3 mL of dichloromethane. A portion of this solution (1 μL) was analysed by chiral G.C. to determine enantioselectivity.[11]

Cryoscopic Molecular Mass   Determination: (using N-methyl ephedrine / diethyl zinc 1:1 as a typical example)

To a Schlenk flask equipped with a side arm and a temperature probe was added a deoxygenated solution of benzene (3.5966 g) containing N-methyl ephedrine (111.4 mg). The entire apparatus was further deoxygenated by three freeze pump thaw cycles. Diethyl zinc (3.10 M in benzene, 0.205 mL) was introduced and the mixture stirred for 10 mins. The apparatus was cooled and the freezing profile determined.

The sensitivity (c) of the temperature probe was calibrated using azobenzene. The molecular mass was determined from the equation:

$$M = (l / L) \times (K / \Delta T)$$

using the temperature probe and substituting ΔT with $c\Delta V$

$$M = (l / L) \times (K / c\Delta V)$$

where M is the molecular mass

l is the mass of ligand in mg

L is the mass of benzene in g

K is the cryoscopic constant for the apparatus (5.12)

ΔT is the freezing depression in Kelvin

c is the sensitivity constant of the temperature probe determined by calibration with azobenzene

ΔV is the voltage difference on freezing depression (mV)

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11   Enantiomeric excesses were determined on crude reaction mixtures using a Hewlett - Packard 5890A gas chromatograph equipped with a 50 m WCOT fused silica capillary GC column coated with CP cyclodextrin-B-2,3,6-M-19 [Chrompack No.7501] and a Hewlett - Packard 3396 Series II integrator. All reactions were performed in duplo and agreed within experimental error (±2%)