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CATALYTIC ASYMMETRIC ALKYLATION OF ALDEHYDES BY DIETHYLZINC IN THE PRESENCE OF *N-iso*-PROPYLEPHEDRINE; DEPENDENCE OF ENANTIOSELECTIVITY ON Et_2Zn:RCHO

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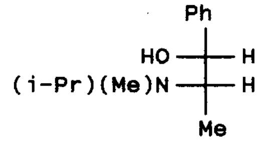
Summary: The enantioselective alkylation of a range of aldehydes by diethylzinc in the presence of N-isopropylephedrine has been investigated. Both the yield and the enantioselectivity of the reaction was found to depend on the ratio of Et_2Zn to the aldehyde.

There has been considerable interest in the enantioselective reactions of dialkylzinc with aldehydes in the presence of chiral amino alcohols [1-4], and we have previously reported the reactions of diethylzinc with benzaldehyde in the presence of a range of *N*-alkylated ephedrines [5]. We now demonstrate that both the chemical and optical yield of these reactions can be dramatically improved by the use of a substantial excess of diethylzinc over the substrate aldehyde, and extend the reaction to a range of different aldehydes.

From earlier work it was clear that the catalyst of choice was 1R,2S-*N-iso*-propyl ephedrine, 1, prepared by a sealed tube alkylation of ephedrine. With a diethylzinc:benzaldehyde:catalyst ratio of 1:1:0.1 optical yields of up to 80 % R had been achieved, at room temperature. The results of concentration dependence experiments for the reaction with benzaldehyde are shown in Table 1. Examination of the data indicates that a good yield is obtained for any Et_2Zn:PhCHO ratio of 2.0 or above. However, the best optical yields were obtained only at molar ratios of 4.0 and above.



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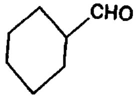

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The preparation of 1-aryl substituted chiral alcohols has been previously achieved in good optical yield by a variety of methods including hydrosilylation [6] and reduction of the ketones with Li[AlH_4] modified by a range of chiral addends [7]. It is therefore of considerable importance that the procedure proposed here should be successful for other types of aldehydes, in particular substrates in which enolisation is possible. The substrates chosen for study were heptanal, cyclohexane carbaldehyde, 2, and cinnamaldehyde. The results of the concentration dependence experiments are shown in Tables 2, 3 and 4. Tables 2 and 3 show the same trends as were observed in the benzaldehyde reactions, with increases in both chemical and optical yields with an increase in Et_2Zn:RCHO ratio.

The results obtained with cinnamaldehyde were generally unsatisfactory, and reproducibilty was poor. It proved necessary to modify our usual isolation and purification procedure (flash chromatography, followed by distillation), since this generally led to the formation of substantial amounts of the acid catalysed elimination product, 1-phenyl-1,3-pentadiene. All extractions and washings used slightly basic solutions, and the final distillation was carried out in the presence of a small amount of solid sodium bicarbonate. The problems in this reaction do not appear to be due to competing conjugate addition of the diaklylzinc, although conjugate addition to enones has been reported in the presence of a nickel salt as catalyst [8]. In the absence of the catalyst less than 5 % of the conjugate addition product was formed. The conjugate addition reactions will be discussed in detail elsewhere.

Table 1 Reactions of diethylzinc with benzaldehyde in the presence of 1

Et_2Zn:PhCHO	Yield[a] %	Optical rotation[b] $[\alpha]_D^{20}$	Optical yield[c] %
1.1	70	+33.8	79.6 R
2.0	98	+34.0	80.0 R
2.5	98.3	+37.4	88.0 R
3.0	98.3	+37.8	89.0 R
4.0	99.8	+40.2	94.6 R
4.5	99.7	+39.8	93.7 R

a by GC (OV-17, 80 °C)

b in benzene

c based on $[\alpha]_D^{20}$ = +42.46 ° (c = 5, benzene), confirmed by ^{31}P nmr spectrsocopy [9]

Table 2 Reactions of diethylzinc with heptanal in the presence of 1

Et_2Zn:RCHO	Yield[a] %	Optical rotation[b] $[\alpha]_D^{20}$	Optical yield[c] %
1.0	75.0	-5.0	60 R
2.0	88.4	-6.56	78.5 R
3.0	92.4	-6.6	79.0 R
4.0	93.7	-6.8	82.0 R

a by GC (OV-17, 80 °C)

b in chlorofom

c based on $[\alpha]_D^{20}$ = -8.36 ° (chloroform) [10], confirmed by ^{31}P nmr spectrsocopy [9]

Table 3 Reactions of diethylzinc with cyclohexane carbaldehyde in the presence of 1

Et_2Zn:RCHO	Yield^a %	Optical rotation^b $[\alpha]_D^{20}$	Optical yield^c %	Optical yield^d %
1.0^e	40	0	0	0
2.5	73.4	+6.5	80.3 R	85.0
3.5	88.5	+7.2	88.8 R	92.3
4.5	89.9	+7.5	97.5 R	97.0

a by GC (OV-17, 160 °C)

b chloroform solution

c based on $[\alpha]_D^{20}$ = +8.1 ° (chloroform) [11]

d based on the results of analytical GC on the mandelate esters [12]

e results from reference 5

Table 4 Reactions of diethylzinc with cinnamaldehyde in the presence of 1

Et_2Zn:RCHO	Yield^a %	Optical rotation^b $[\alpha]_D^{20}$	Optical yield^c %
2.0	85.2	+0.9	13.6 R
3.0	85.4	+1.2	18.2 R
4.0	80.0	+1.5	22.7 R

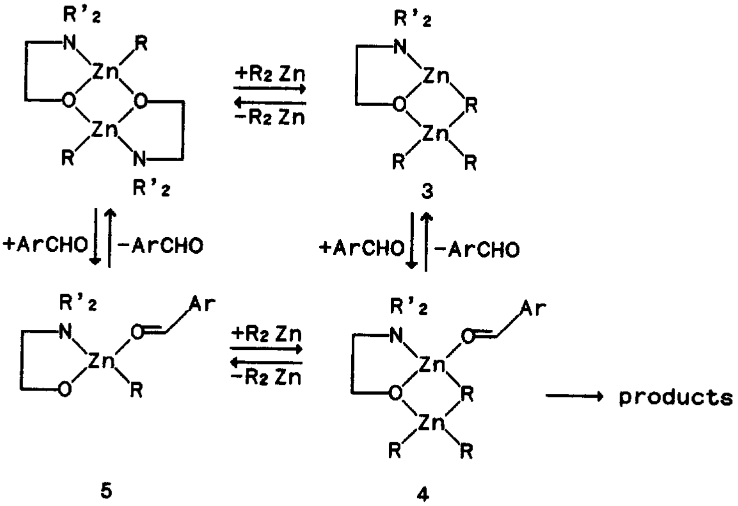
a by GC (OV-17, 160 °C)

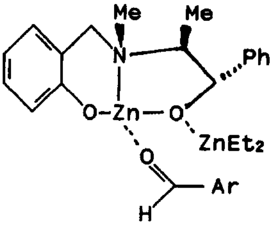
b chloroform solution

c based on $[\alpha]_D^{23}$ = 6.6 ° ($CHCl_3$)

It is pertinent to consider these results in the light of the reaction mechanism proposed by Noyori [1]. He proposes that the key reacting intermediate is 5, which is formed by an equilibrium with 3 or 4. It is clear that the position of the equilibrium, and hence the concentration of the reactive species, will be effected by the excess of diethylzinc present, thus accounting for the effect of the dialkylzinc concentration on the yield. If we assume that alkylation reactions may occur, though perhaps less rapidly, through other intermediates, it is reasonable to suppose that these may be less enantioselective. Thus, a high concentration of 5 will also ensure a high enantioselectivity. It is reasonable to suppose that the positions of the equilibria in this system will depend on the nature of the chiral amino alcohol ligand, and hence the concentration dependence of the outcome may be substantial, as in this case, or less obvious, as observed elsewhere. We should note, that under our conditions, (room temperature, 48 h) there is a significant uncatalysed alkylation reaction (65 % yield). At the lower temperature used by Noyori (0 °C), no uncatalysed alkylation was observed, but instead a slow reduction to benzyl alcohol. Under our conditions no benzyl alcohol may be detected in the products, in the presence or absence of the catalyst.

We should further note that when *N*-3-hydroxypropylephedrine was used as the catalyst, there was no significant dependence of either chemical (90 %) or optical (72 %) yield on the Et_2Zn:PhCHO ratio [13]; in this case we would expect the complete formation of an intermediate, closely related in structure to 6, postulated by Corey [14], with attack by more or less strongly associated diethylzinc.





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References

1 M. Kitamura, S. Okada, S. Suga and R. Noyori, *J. Am. Chem. Soc.*, 111 (1989) 4028.
2 K. Soai, S. Niwa and M. Watanabe, *J. Org. Chem.*, 53 (1988) 927.
3 K. Soai, S. Niwa and T. Hatanaka, *J. Chem. Soc., Chem. Commun.*, (1990) 709.
4 S. Jtsuno and J.M.J. Frechet, *J. Org. Chem.*, 52 (1987) 4140.
5 P.A. Chaloner and S.A.R. Perera, *Tetrahedron Lett.*, 28 (1987) 3013.
6 D. Valentine and J.W. Scott, *Synthesis*, (1978) 329.
7 R. Noyori, *Pure Appl. Chem.*, 53 (1981) 2316.
8 K. Soai, T. Hayasaka, S. Ugayin and S. Yokoyama, *Chem. Lett.*, (1988) 1571.
9 B.L. Feringa, A. Smaardijk and H. Wynberg, *J. Am. Chem. Soc.*, 107 (1985) 4798.
10 M. Kitamura, S. Suga, K. Kawai and R. Noyori, *J. Am. Chem. Soc.*, 108 (1986) 6071.
11 E.P. Burrows, F.J. Welch and H.S. Mosher, *J. Am. Chem. Soc.*, 82 (1960) 880.
12 H.C. Rose, R.L. Stern and B.L. Karger, *Anal. Chem.*, 38 (1966) 469.
13 P.A. Chaloner and E. Langadianou, to be published
14 E.J. Corey and F.J. Hannon, *Tetrahedron Lett.*, 28 (1987) 5237.

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