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CHIRAL CATALYSIS IN THE ALKYLATION OF ALDEHYDES WITH DIETHYL ZINC

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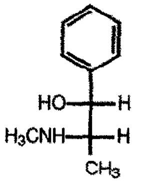
Abstract: The reaction of diethyl zinc with benzaldehyde and ephedrine derived catalysts was investigated. It was found that O-alkylated ephedrine could act as a catalyst for the reaction, but that the reaction was no longer stereoselective to the same degree as for the ephedrine catalysed reaction.

Alkylation of carbonyl compounds using organometallic reagents is a reaction which has received extensive attention over the years. Recently, interest has spread to include reactions which are stereoselective, giving moderate to good enantiomeric excess at the new stereogenic centre.[1,2] Early examples of this type of reaction required one or more equivalents of the chiral moderator, and were therefore wasteful in terms of chirality. Later developments of this type of reaction used a chiral moderator in catalytic quantities.[3-6] The optical yields could be maintained whilst the amount of chiral substances consumed was greatly reduced. One such reaction is the alkylation of aldehydes with diethyl zinc in the presence of catalytic quantities of α,β-hydroxy amines.[6-13]

Aldehydes and ketones are normally inert to treatment with diethyl zinc under simple reaction conditions. However, if a small amount of an α,β-hydroxy amine is present, quantitative conversion to a secondary or tertiary alcohol can be achieved. If the α,β-hydroxy amine is chiral, as in (-)-ephedrine (**1**) or DAIB (**2**), an enantiomeric excess of up to 98% can be obtained in the product.[6-13]



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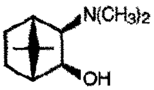

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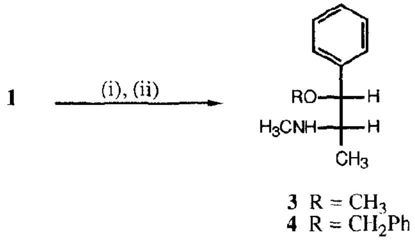
This reaction has been investigated by a number of people, most noticeably by Noyori and coworkers.[6] Their conclusions, based on kinetic and X-ray crystallographic data are that a number of complexes are involved in the catalytic cycle, one of these complexes contains two molecules of the catalyst. The probability of obtaining such a complex, and thus achieving the desired reaction, should be greatly enhanced if the components could be brought together more effectively. Soai et al. considered this possibility and linked two ephedrine molecules together with a propyl chain attached to the amine functions. This gave a catalyst which slightly improved stereoselectively.[9]

We have been interested in developing the ideas of Soai et al. in order to obtain a catalyst conferring greater stereoselectivity, which may also be used in reactions with non benzylic aldehydes and ketones.

Ephedrine molecules may be linked by three methods, either through the amine, the hydroxyl or by the creation of new carbon carbon bonds. The last of these methods seems to be the least attractive at this point in time. The work of Soai used compounds linked through the amine functions. We therefore turned our attention to compounds linked through the hydroxyl functions. It was decided first to study the effect of derivatising the alcohol function on the catalytic reaction. If the catalytic activity is lost for simple ethers then it may not be fruitful to pursue this approach further. A study of the reaction of diethyl zinc with benzylic aldehydes in the presence of ephedrine ethers was carried out . It was found that whilst the catalytic activity for the reaction remained, the product was no longer formed stereoselectively.

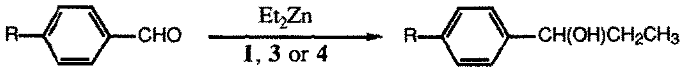
Results and discussion. The catalysts tested were ephedrine, **1**, O-methyl ephedrine **3**, and O-benzyl ephedrine **4**. Compounds **3** and **4** were synthesised from (-)-ephedrine in good yields following the procedure of Meyers et al.[14] (Scheme 1), physical data agreed with those reported previously.[15]



Scheme 1: (i) KH, (ii) CH_3I for **3**, $PhCH_2Br$ for **4**

As substrates for the alkylation reactions benzaldehyde, **5a**, 4-methyl benzaldehyde, **5b** and 4-methoxy benzaldehyde, **5c**, were chosen. These aldehydes were treated with diethyl zinc in the presence of a catalytic amount of the catalyst following the procedure described by Soai et al. (Scheme 2). After completion of the reaction, the products **6a** - **c** were isolated by column chromatography on silica gel.

Reaction times were found to be much shorter when the ether derivatives of ephedrine were used as catalysts, high yields were obtained in all cases. The enantiopurity of the products was then determined using phosphorus NMR.[16,17] This method of measurement is reliable to within 2% e.e. for mixtures close to racemic. Consequently some of the entries in Table 1 can be considered to represent racemic mixtures whilst others represent small but significant enantiomeric excesses.



5a R = H
5b R = CH_3
5c R = OCH_3

6a R = H
6b R = CH_3
6c R = OCH_3

Scheme 2

Table 1

The reaction of aryl aldehydes with diethyl zinc.

Substrate	Catalyst	Reaction Time [h]	Yield [%]	%e.e.
5a	**1**	36	90	60
5b	**1**	48	88	65
5c	**1**	48	75	56
5a	**3**	4	90	2
5b	**3**	3	95	4
5c	**3**	4	80	5
5a	**4**	4	80	7
5b	**4**	5	85	2
5c	**4**	5	80	2

It has been shown that ephedrine acts as a stereoselective catalyst for the reaction of diethyl zinc with benzylic aldehydes.[7] The ether derivatives presented herein also catalyse this reaction to at least the same extent, although without the stereoselectivity. It seems obvious that the loss of ability for chiral induction is related to the alkylation of the alcohol. However, it is not clear whether this is due the change in the ligand forming properties of the oxygen atom, or to steric interference caused by the alkyl group. We conclude that the hydroxyl group is not a prerequisite for the catalytic activity of ephedrine in the diethyl zinc alkylation of aldehydes, but that it is necessary for the stereoselectivity of the reaction.

Experimental section: (-)-Ephedrine (e.e. = 100 %) was purchased from Apoteksbolaget, Göteborg Sweden. All other chemicals were of reagent grade, the aldehydes and solvents were distilled before use. ^1H, ^{13}C and ^{31}P-NMR spectra were recorded on either a JEOL FX90Q or a JEOL EX270 spectrometer.

O-alkylation of ephedrine. General procedure: A round bottomed flask was charged with potassium hydride (1.75g, 43.6 mmol), tetrahydrofuran (100 ml) and a large magnet for efficient stirring.

(-)-Ephedrine, **1**, (4.86g, 29.4 mmol) in tetrahydrofuran (100 ml) was added dropwise over 1h. The mixture was stirred for 16h. after which the alkyl halide (28 mmol) in tetrahydrofuran (50 ml) was added. After a further 3h. the reaction was carefully quenched by addition of ice cold water (400 ml), and the product extracted with diethyl ether (3 x 150 ml). The combined ether phases were concentrated to a yellow oil and purified on silica gel using stepwise increments of concentration of ethanol in dichloromethane. The O-alkyl ephedrine derivatives eluted with an ethanol concentration of 30%.

O-Methyl ephedrine 3. Yield 70%.

^{1}H-NMR (89.55 MHz): δ 7.32 (m, 5H), 4.15 (d, J = 5.1 Hz, 1H), 3.26 (s, 3H), 2.73 (m, 1H), 2.38 (s, 3H), 1.03 (d, J = 6.4 Hz, 3H).

^{13}C-NMR (22.15 MHz): δ 141 4, 128.2, 127.1, 126.8, 84.6, 65.3, 56.8, 41.9, 8.2.

O-Benzyl ephedrine 4. Yield 75%.

^{1}H-NMR (270.05 MHz): δ 7.32 - 7.19 (m, 10H), 4.43 (d, J = 11.7 Hz, 1H), 4.28 (d, J = 5.3 Hz, 1H), 4.18 (d, J = 11.7 Hz, 1H), 2.69 (m, 1H), 2.23 (s, 3H), 1.00 (d, J = 6.6 Hz, 3H).

^{13}C-NMR (67.80 MHz): δ 139.7, 138.4, 128.4, 128.3, 127.7, 127.6, 127.4, 127 3, 83.4, 70.7, 59.9, 33.7, 14.9.

Reaction of aldehydes with diethyl zinc in the presence of a catalyst.

General procedure: The ephedrine derivative (0.05 eq.) was dissolved in hexane in a three necked round bottomed flask fitted with a rubber septum and under an inert atmosphere. Diethyl zinc (2.2 eq.) was slowly injected and the resulting solution cooled to 0 °C. The aldehyde (1.0 eq.) in hexane was slowly injected. The stirred reaction mixture was monitored by GC. Upon completion of the reaction, ethanol (5 ml / mmol aldehyde) was added followed by water (20 ml / mmol aldehyde). This mixture was extracted with hexane and diethyl ether and the combined organic phases concentrated to an oil. The product was purified by chromatography on silica gel eluting with petroleum ether and dichloromethane. The products isolated in this manner were analysed by ^{31}P-NMR to determine the enantiopurity. The results obtained are presented in table 1.

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