Stereoselective Addition Reaction of Diethylzinc to Aldehydes, Catalyzed by Cinchona Alkaloids

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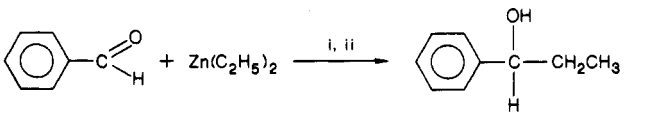
The cinchona alkaloid catalyzed reaction of diethylzinc and aldehydes leads to optically active alcohols having enantiomeric excesses up to 92%.

The reaction of organometallics with carbonyl compounds is a well-studied carbon–carbon bond-forming reaction.[1-5] Since the products are often asymmetric, many attempts have been made to perform this reaction with optical induction. In some cases, high enantiomeric excesses have indeed been obtained. The method used to obtain these optical inductions is the introduction of a chiral ligand, which complexes with one or more participants in the reaction. A disadvantage of these enantioselective reactions is the necessity of using one or more equivalents of chiral ligand. The reasons for using a stoichiometric amount of ligand, necessary to obtain the highest optical yield are (1) some organometallics are able to react with carbonyls even in the absence of a ligand, (2) the chiral ligand complexed with a reagent acts as a chirality transfer agent only once [It exhibits no turnover like a real catalyst.], and (3) the rate of complexation between ligand and substrate molecule(s) is not faster than the rate of a reaction between uncomplexed substrates.

To date only one enantioselective addition reaction involving organometallics has been reported in which only catalytic amounts of a chiral agent can be used to obtain a moderate optical yield.[16] This is the reaction between diethylzinc and benzaldehyde, catalyzed by either camphoric complexes of cobalt or palladium[6] or primary 2-amino-1-alcohols.[7] However, these catalysts have to be synthesized.[8] Furthermore, the amino alcohols used are derivatives of amino acids, natural products of which only one enantiomer is readily available. As a consequence of this, only products enriched in one enantiomer can be synthesized, since the configuration of the catalyst determines the configuration of the product. The major cinchona alkaloids (Figure 1) are also amino alcohols of which several diastereomers are available. Furthermore, these compounds are not primary but tertiary amines, able to form stable complexes with dialkylzinc compounds.[9] The rigid structure of this quinuclidine part makes the nitrogen atom suitable for complex formation.

Scheme I[a]



$[\alpha]^{20}_{D}$ +27.2° (c 1, toluene)
ee 68%[15]

[a] (i) 2% quinine; toluene; 20 °C; 24 h; (ii) HCl/H_2O.

When the addition of diethylzinc to benzaldehyde in toluene at 20 °C was performed in the presence of a catalytic amount of quinine (2 mol %), optically active (*R*)-(+)-1-phenyl-propanol with an ee of 68% could be isolated in 92% yield (Scheme I).

This result was particularly encouraging, since it was the highest enantiomeric excess ever obtained in a catalytic enantioselective addition reaction of an organometallic to a carbonyl compound. In order to obtain more insight into the steric course of this reaction, the reaction was investigated under different conditions, with different reagents. The results of these experiments are given in Table I. From this table, several conclusions can be drawn: (1) The configuration of the product formed in excess depends upon the cinchona alkaloid employed (entries 1–4). In agreement with all cinchona alkaloid catalyzed reactions reported to date,[12] the configuration of the carbon atom C-8 and C-9 of the catalyst determines the configuration of the product formed in excess. (2) A quinine-catalyzed reaction (entry 1) gave a remarkably higher ee with respect to a quinidine (entry 2) catalyzed reaction. The only difference between these catalysts is the configuration of C-8 and C-9. As a consequence of this, the vinyl group is oriented differently. Therefore this vinyl function is probably directly involved in the mechanism. The result of a dihydroquinine-catalyzed reaction (entry 11) supports this hypothesis. (3) The presence of the 6′-methoxy group seems of lesser importance. Although a cinchonidine-catalyzed reaction (entry 3) gave a somewhat lower ee than a quinine-catalyzed reaction (entry 1), the ee's obtained on use of quinidine (entry 2) and cinchonine (entry 4) were comparable. (4) Remarkable differences in ee are obtained between a quinine (entry 5) and acetylquinine (entry 10) catalyzed reaction. Thus the hydroxyl function is important in order to obtain a high enantiomeric excess.[12] (5) An increase of ee, up to 92%, is obtained by the use of *o*-alkoxybenzaldehydes instead of benzaldehyde. Introduction of a methoxy group at the para position (entry 6) leads to an ee comparable to a reaction involving benzaldehyde. A second methoxy group at the meta position

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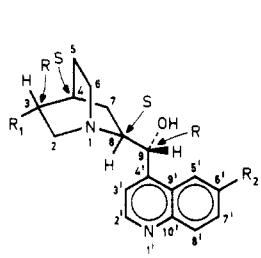
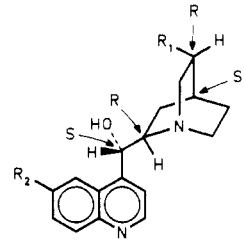
Table I

entry	aldehyde	catalyst	solvent	yield[a] (%)	$[\alpha]^{20}_D$, deg (c 1, toluene)	ee (%)	conf formed in excess
1	benzaldehyde	quinine	toluene	92	+27.2	68	*R*
2	benzaldehyde	quinidine	toluene	90	−19.2	48	*S*
3	benzaldehyde	cinchonidine	toluene	89	+23.0	58	*R*
4	benzaldehyde	cinchonine	toluene	90	−18.4	46	*S*
5	*o*-methoxybenzaldehyde	quinine	toluene	83	+44.9	83	
6	*p*-methoxybenzaldehyde	quinine	toluene	73	+20.4	61	
7	2,5-dimethoxybenzaldehyde	quinine	toluene	80	+27.7	84	
8	*o*-ethoxybenzaldehyde	quinine	toluene	72	+47.3	92	
9	dihydrocinnamic benzaldehyde	quinine	toluene	60	−10.6[b]	40	
10	*o*-methoxybenzaldehyde	acetylquinine	toluene	78	+7.4	14	
11	*o*-methoxybenzaldehyde	dihydroquinine	toluene	40[c]	+25.7	48	
12	*o*-methoxybenzaldehyde	quinine	Et_2O	87	+47.0	87	
13	*o*-ethoxybenzaldehyde	quinine	Et_2O	90	+45.0	90	

[a] After bulb-to-bulb distillation. [b] *c* 1, EtOH. [c] After 24 h only 77% conversion.





	R_1	R_2
quinine	C_2H_3	OCH_3
cinchonidine	C_2H_3	H
dihydroquinine	C_2H_5	OCH_3
dihydrocinchonidine	C_2H_5	H

	R_1	R_2
quinidine	C_2H_3	OCH_3
cinchonine	C_2H_3	H
dihydroquinidine	C_2H_5	OCH_3
dihydrocinchonine	C_2H_5	H

Figure 1. Structure, numbering, and absolute configuration of the eight major cinchona alkaloids.

(entry 7) did not lead to an increase of enantiomeric yield, with respect to a reaction with *o*-methoxybenzaldehyde (entry 5). Increase of the bulk of the ortho substituent, by introduction of an ethoxy group (entry 8) instead of a methoxy group (entry 5), gave a higher ee. On the basis of these results, the influence of the ortho substituent on the ee arises from a steric rather than an electronic effect. (6) The result of using dihydrocinnamic aldehyde (entry 9) shows that the enantioselective diethylzinc addition is not limited to arylaldehydes but is also applicable to aliphatic aldehydes. (7) Reactions in diethyl ether (entries 12, 13) proceeded comparable to reactions in toluene. Thus the solvent effect, on changing from toluene to diethyl, was minor.

An uncatalyzed reaction of diethylzinc with both benzaldehyde and *o*-methoxybenzaldehyde in toluene was rather slow. In the case of benzaldehyde the conversion was 30% after 24 h, whereas *o*-methoxybenzaldehyde gave 48% conversion.

Diethyl ether as solvent gave the same result. An uncatalyzed reaction between *o*-methoxybenzaldehyde and diethylzinc gave 52% conversion. Thus in both toluene and diethyl ether, some competition between an uncatalyzed and a catalyzed reaction exists.

On the basis of the results as given in Table I, placing the diethylzinc molecule in the quinuclidine part of the quinine seems reasonable. In this situation, as shown in Figure 2, the hydroxyl group of the catalyst is available for hydrogen bonding with the carbonyl function of the aldehyde. This explains why an acetylquinine-catalyzed reaction proceeds analogously to a quinine-catalyzed reaction, but with a large decrease of enantiomeric yield. In both cases the diethylzinc is identically oriented and activated, but the benzaldehyde is not. In the case of quinine, where a high ee was obtained, the hydrogen provides a rigid orientation of the benzaldehyde, whereas in an acetylquinine-catalyzed reaction this orientation is lost. The transition state of Figure 2 leads to product with the *R* configuration. Since in a quinine-catalyzed reaction benzaldehyde leads to 1-phenyl-1-propanol in a ratio *R*:*S* of 84:16, the proposed transition state is in agreement with this result.

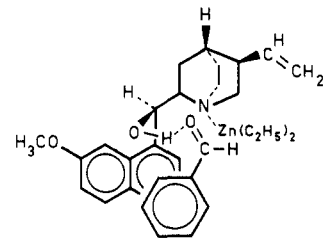


Figure 2.

The vinyl group of the catalyst proves to be important to obtain a good optical and chemical yield. Therefore an interaction of diethylzinc and this vinyl group is postulated. Zinc is a main group metal, but coordination of a main group metal to olefins is possible. Furthermore, π-donating interaction of diethylzinc with π-donor groups as benzene has been suggested.[13] In the transition state of Figure 2, an interaction of the vinyl group and diethylzinc might be possible. An interaction with the vinyl group of a second catalyst molecule is also imaginable. Another possibility is that the vinyl group directs the diethylzinc into the quinine molecule, before the transition state is reached. further spectroscopic study of the structures of the reaction intermediates should clarify the role of the vinyl group.

None of the alkoxy-substituted alcohols have been reported in optically active form prior to this work. Therefore the absolute configurations of these alcohols are unknown. For this reason, the reactions starting from

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(15) The enantiomeric excesses of this and other alcohols were determined by both a reaction with PCl_3[10] and by their Mosher derivatives.[11] In all cases, the obtained ee's, as determined by both methods, gave the same value (within 2%). In some cases no base-line separation of the ^{19}F NMR signals of the Mosher derivatives was obtained. However, with PCl_3, well-resolved signals were always found.

(16) **Note Added in Proof**: After acceptance of our paper, the fine publication of Kitamura et al. (Kitamura, H.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071) appeared. Using nonalkaloid amino alcohols as catalyst, their results equal or better ours.

alkoxy-substituted benzaldehydes were not involved in the discussion of the transition state. Based on the obtained results, it is likely that these alcohols were formed via the same mechanism.

Experimental Section

General Remarks. Reactions with diethylzinc were performed in a dry nitrogen atmosphere by using Schlenk-type glassware. Diethylzinc is commercially available. For the experiments a standard toluene solution, containing 0.3 g/mL diethylzinc was prepared. The aldehydes are all commercially available. They were distilled just before use.

General Procedure for the Addition of Diethylzinc to Aldehydes. In a carefully dried Schlenk vessel was placed a 15-mL toluene solution containing 7 mmol of aldehyde. To this magnetically stirred solution was added 50 mg of the catalyst, followed by slow injection (10 min) of 4 mL of a toluene solution containing 0.3 g/mL diethylzinc. This mixture was stirred overnight. The mixture was cooled to 0 °C by an ice–salt bath and 10 mL of 1 N HCl was slowly added (10 min) with continuous stirring. The toluene layer was separated and subsequently washed with 2 × 8 mL of 1 N HCl. After drying over Na_2SO_4 and filtration, the toluene was removed under reduced pressure. The crude alcohol was purified by bulb-to-bulb distillation under reduced (oil pump) pressure. The isolated yield was between 70 and 90%. The products were characterized by ^1H NMR spectroscopy and derivatized with PCl_3 and Mosher reagent for enantiomeric excess determination when necessary.

1-Phenyl-1-propanol: $[\alpha]_D^{20}$ +27.2° (*c* 1, toluene), ee 68%; ^1H NMR δ 0.9 (t, 6 Hz, 3 H), 1.4–2.0 (m, 2 H), 2.1 (br s, 1 H), 4.5 (t, 7 Hz, 1 H), 7.1–7.4 (m, 5 H).

1-(*o*-Methoxyphenyl)-1-propanol: $[\alpha]_D^{20}$ +47.0° (*c* 1.2, toluene), ee 87%; ^1H NMR δ 0.8 (t, 7 Hz, 3 H), 1.4–2.0 (m, 2 H), 2.6 (br s, 1 H), 3.6 (s, 3 H), 4.7 (t, 7 Hz, 1 H), 6.6–7.3 (m, 4 H).

1-(*p*-Methoxyphenyl)-1-propanol: $[\alpha]_D^{20}$ +20.4° (*c* 1.2, toluene), ee 61%; ^1H NMR δ 0.9 (t, 8 Hz, 3 H), 1.5–2.0 (m, 2 H), 2.1 (s, 1 H), 3.7 (s, 3 H), 4.4 (t, 7 Hz, 1 H), 6.6–7.3 (m, 4 H).

1-(2,5-Dimethoxyphenyl)-1-propanol: $[\alpha]_D^{20}$ +27.7° (*c* 1.2, toluene), ee 84%; ^1H NMR δ 0.9 (t, 7 Hz, 3 H), 1.4–2.0 (m, 2 H), 2.7 (br s, 1 H), 3.7 (s, 6 H), 4.7 (t, 7 Hz, 1 H), 6.6–6.9 (m, 3 H).

1-(*o*-Ethoxyphenyl)-1-propanol: $[\alpha]_D^{20}$ +46.3° (*c* 1.2, toluene), ee 92%; ^1H NMR δ 0.9 (t, 7 Hz, 3 H), 1.4 (t, 7 Hz, 3 H), 1.6 (m, 2 H), 2.8 (br s, 1 H), 4.0 (q, 7 Hz, 2 H), 4.7 (t, 7 Hz, 1 H), 6.4–7.3 (m, 4 H).

1-Phenyl-3-pentanol: $[\alpha]_D^{20}$ −10.6° (*c* 1, EtOH), ee 40%; ^1H NMR δ 0.9 (t, 7 Hz, 3 H), 1.3–2.0 (m, 5 H), 2.4–2.9 (m, 2 H), 3.3–3.7 (m, 1 H), 7.0–7.3 (m, 5 H).

Synthesis of the Enantiomeric K-Region Arene 5,6-Oxides Derived from Chrysene, 7,12-Dimethylbenz[*a*]anthracene, and Benzo[*c*]phenanthrene

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K-region arene 5,6-oxides of chrysene, benzo[*c*]phenanthrene [B[*c*]Ph], and 7,12-dimethylbenz[*a*]anthracene (DMBA) have been synthesized from resolved *cis*-5,6-dihydrodiols by the ortho ester route as well as from separated bromo(menthyloxy)acetate precursors in the cases of chrysene and B[*c*]Ph. Absolute configurations of the 5,6-oxides and their precursors from chrysene and DMBA have been determined by nucleophilic trans addition of methanol to the oxirane ring and correlation by circular dichroism of the adducts with trans dihydrodiols of known configurations. Confirmation of the configurational assignments to the enantiomeric chrysene *cis*-5,6-dihydrodiols was achieved by reduction to *cis*-5,6-dihydroxy-1,2,3,4,5,6-hexahydrochrysene and determination of the skew sense of the resulting biphenyl chromophore through CD measurements. B[*c*]Ph 5,6-oxide enantiomers were assigned by direct comparison with a sample of known configuration on a chiral column.

Optically active arene oxides of known absolute configuration are of substantial interest in that they can be used to define the stereoselectivity of the hepatic cytochromes P450 which form such metabolites and to establish the mechanism and enantioselectivity of nonoxidative drug metabolizing enzymes such as microsomal epoxide hydrolase and glutathione *S*-transferases which utilize arene oxides as substrates. K-region arene oxides are particularly useful in this regard since they are stable and have very low solvolytic reactivity[1] and since they are not subject to spontaneous racemization.[2] Thus, cytochrome P450c either in liver microsomes from 3-methylcholanthrene-treated rats or in homogeneous preparations has been shown to display high stereoselectivity in the formation of enantiomeric K-region arene oxides from benzo[*a*]pyrene, benz[*a*]anthracene, and 7,12-dimethylbenz[*a*]anthracene.[3] A steric model for the catalytic binding site of this enzyme has been proposed,[4] and the metabolism of chiral K-region arene oxides has been examined with microsomal epoxide hydrolase[5] and gluta-

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