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Catalytic Enantioselective Addition of Diethylzinc to (Hetero)Aromatic Aldehydes

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The asymmetric alkylation with diethylzinc of five heterocyclic aldehydes and benzaldehyde (for comparison) has been studied in the presence of two optically active amino alcohols: (*S*)-2-amino-1-butanol (AB) and (1*S*,2*R*)-*N*,*N*-dibutylnorephedrine (DBNE). A number of chiral (hetero)aromatic secondary alcohols were synthesized in high yields (95–98%) with enantioselectivity up to 92% enantiomeric excess (*ee*) in the presence of DBNE catalyst. Optically active thienyl and 4-pyridyl derivatives were prepared for the first time by catalytic asymmetric alkylation. The influence of the amount of DBNE on the enantioselectivity was investigated. In contrast to benzaldehyde, 2-furan- and 2-thiophene-carbaldehydes, in the case of 3- and 4-pyridinecarbaldehydes the *ee* values depend directly on the catalyst concentration. © **1998 John Wiley & Sons, Ltd.**

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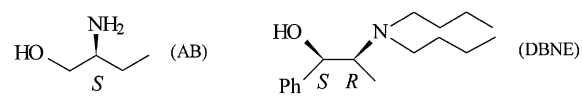
INTRODUCTION

Optically active heteroaryl alkyl alcohols are important synthetic intermediates.[1–4] In continuation of our previous investigation of the enantioselective synthesis of valuable (hetero)aromatic optically active compounds (carbinols, cyanohydrins etc.) by asymmetric catalytic hydrosilylation and hydrogen-transfer reduction of ketones and trimethylsilylcyanation of aldehydes,[5,6] we are reporting here the preparation of chiral heterocyclic carbinols using the addition of diethylzinc to the corresponding aldehydes (some of these results was reported in Ref. 7).

The addition of organometallic reagents to aldehydes under chiral catalysis was proposed as a convenient method for the preparation of various chiral secondary alcohols (for the recent reviews and papers, see Refs 8–14). A vast number of chiral compounds (protic electron-donor chelating ligands) were tested as catalysts for these reactions (camphor derivatives, amino alcohols, cinchona alkaloids, proline-containing substances, ephedrine and its derivatives, as well as the optically active metal complexes etc). Scheme 1 (according to Noyori[11]) illustrates a route for enantioselective alkylation of aromatic aldehydes using a small amount of a chiral source.

To study the enantioselective alkylation with Et_2Zn of N-, S- and O-heterocyclic compounds (2-, 3-, 4-pyridine-, 2-thiophene- and 2-furan-carbaldehydes) we have chosen two optically active *β*-amino alcohols: (*S*)-2-amino-1-butanol (AB) and (1*S*,2*R*)-*N*,*N*-dibutylnorephedrine (DBNE).



The alkylation of benzaldehyde was studied for comparison with heterocyclic aldehydes under the same reaction conditions. In the literature the addition of Et_2Zn to heterocyclic aldehydes is described only for 2-furaldehyde and 3-pyridinecarbaldehyde,[15–17] both catalysed with DBNE.

EXPERIMENTAL

General procedure

The catalyst (0.02–1 mmol; see Table 1), 2.2 ml of dry toluene and aldehyde (1 mmol) were placed in a flame-dried Schlenk tube under an argon atmos-

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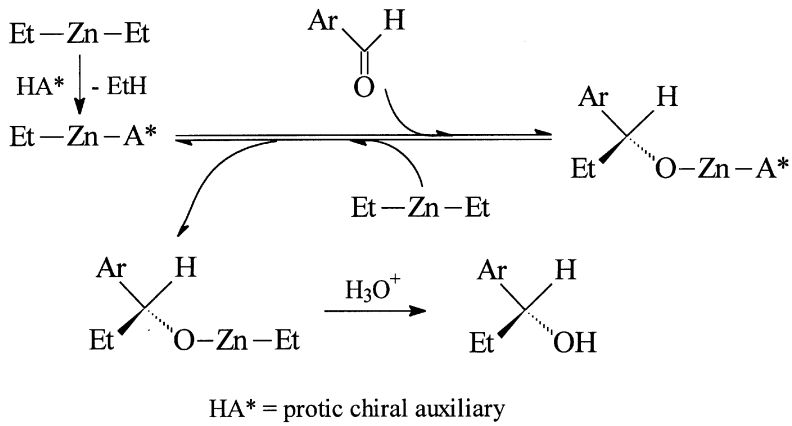


Scheme 1 Principle of chiral alcohol synthesis by catalytic asymmetric addition of diethylzinc to aromatic aldehydes.

phere. The mixture was stirred at room temperature for 15 min, then cooled to 0 °C, and 2.2–2.7 ml of 1 M diethylzinc (2.2–2.7 mmol) solution in hexane was added. The reactions were carried out at 0 °C or were warmed to 9 °C (the temperature of the refrigerator). After almost complete conversion of aldehyde (monitoring by GC), the reaction was quenched by the addition of saturated NH_4Cl solution at 0 °C for 2 h. The organic layer was separated and analysed by means of GC, GC–MS and chiral GC.

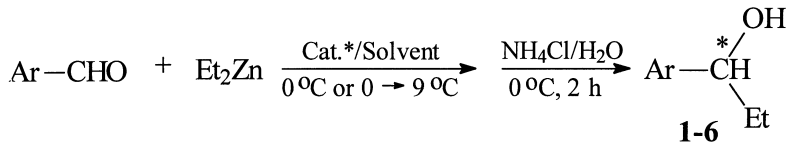
Materials and Methods

Toluene was distilled from $LiAlH_4$ before use. Diethylzinc (1 M solution in hexane), (*S*)-(+)-2-amino-1-butanol and (1*S*,2*R*)-(−)-2-dibutylamino-1-phenyl-1-propanol (*N*,*N*-dibutyl-D-norephedrine)

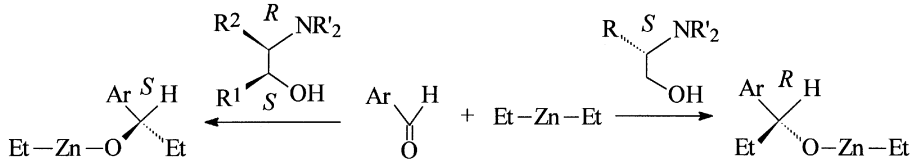
Table 1 Enantioselective addition of Et_2Zn to (hetero)aromatic aldehydes followed by hydrolysis

Entry	Ar	Catalyst (amount, mol%)	Reaction time (h)	Aldehyde conversion, GC (%)	Chiral alcohol		
					Chemical yield, GC (%)	*ee*,[a] GC (%)	Configuration
1[b,d]	Ph	AB (4)	44	87	72	53	*R*
2[b,d]	Ph	DBNE (2)	44	100	100	90	*S*
3[c,d]	Fur	AB (8)	44	90	83	36	*R*
4[c,d]	Fur	DBNE (6)	70	98	96	86	*S*
5[c,d]	Th	AB (8)	44	79	55	38	*R*
6[c,d]	Th	DBNE (6)	70	100	98	92	*S*
7[c,d]	2-Py	DBNE (6)	20	100	95	2	*S*
8[b,e]	2-Py	DBNE (72)	6	96	81	2	*S*
9[b,d]	3-Py	AB (20)	20	96	78	11	*R*
10[b,d]	3-Py	DBNE (6)	20	100	99	32	*S*
11[b,e]	3-Py	DBNE (40)	8	100	98	55.5	*S*
12[b,e]	3-Py	DBNE (68)	6	100	98	73	*S*
13[b,e]	4-Py	AB (38)	20	67	65	2.5	*R*
14[b,d]	4-Py	DBNE (14.4)	6	100	100	22	*S*
15[b,d]	4-Py	DBNE (25)	6	100	98	28,28[f]	*S*
16[b,e]	4-Py	DBNE (29)	6	100	98	30	*S*
17[b,e]	4-Py	DBNE (43.2)	6	100	98	36	*S*
18[b,e]	4-Py	DBNE (72)	6	100	96	43	*S*
19[b,e]	4-Py	DBNE (100)	6	100	97	57.5	*S*

[a] Detected by means of chiral GC (see Table 2). [b,c] Reactions were carried out at 0 °C or 0 → 9 °C, respectively. [d,e] Molar ratio of aldehyde and Et_2Zn = 1:2.2 or 1:2.6–2.7, respectively. [f] Analyses were performed with two different columns: Lipodex E and Chirasil-Dex CB.



Scheme 2 Catalytic asymmetric alkylation of aldehydes by Et_2Zn: Ar = Ph, 2-furyl (Fur), 2-thienyl (Th), 2-, 3-, 4-pyridyl (Py); Cat* = (*S*)-2-amino-1-butanol or (1*S*,2*R*)-*N*,*N*-dibutylnorephedrine; Solvent = hexane, toluene.



Scheme 3 Examples of asymmetric induction rules for alkylation of aromatic aldehydes by Et_2Zn.

were purchased from Fluka. The aldehydes (Merck) were distilled before use.

GC analysis was performed on an HP 5880-A chromatograph, equipped with a flame-ionization detector, on a capillary column packed with SE-54 phase (25 m × 0.2 mm), the carrier gas was helium (1 ml min^{-1}). GC–MS spectra were obtained using an HP 5890 (II) chromatograph on an HP 101 capillary column (Polydimethylsiloxane, 25 m × 0.2 mm), connected to an HP Engine 5989-A mass spectrometer (70 eV). The chiral separations were performed on an HP 5890 (II) gas chromatograph with the Macherey–Nagel capillary columns containing various chiral phases: Cyclodex IP (50 m × 0.2 mm), Lipodex E (25 m × 0.2 mm), Chirasil-Dex CB (25 m × 0.2 mm).

RESULTS AND DISCUSSION

The enantioselective addition of diethylzinc to benzaldehyde had been studied previously in the presence of a large number of chiral catalysts, including AB[18] and DBNE.[19] 1-Phenyl-1-propanol (**1**) was obtained[18] in 97% yield with 26% enantiomeric excess (*ee*) (*R*-configuration) by the reaction of benzaldehyde with Et_2Zn (1.0 equiv) in toluene in the presence of AB (2 mol%) at 20 °C for 41 h. This chiral carbinol was synthesized[19] in quantitative yield, and 90% *ee* (*S*-configuration) by means of Et_2Zn (2.2 equiv) in hexane at 0 °C for 16 h in the presence of DBNE (6 mol%). This process served as a model reaction for the synthesis of carbinol **1** having the known configuration necessary for the chiral GC analysis. GC chiral resolutions of product **1** were performed on a column (50 m) packed with Cyclodex IP chiral chromatographic phase at 120 °C. Chiral alcohol **1** was prepared in 72% and 100% chemical yield and 53% (*R*) and 90% (*S*) *ee*, respectively, in the presence of AB and DBNE catalysts under the reaction conditions being studied (Scheme 2; Table 1, Ar = Ph, entries 1 and 2).

It is known that the geometry of the chiral catalyst determines the absolute configuration of the predominantly formed enantiomer, regardless of the aldehyde used for the addition reaction. The rules given in Scheme 3 indicate that the α-*S*- or β-*R*-configuration of β-dialkylamino alcohols consistently produces the *S*-alcohol, whereas the β-*S*-configuration of a catalyst forms the *R*-enantiomer. The prevailing absolute configuration is determined primarily by that of the hydroxyl-containing α asymmetric carbon of the amino alcohols. This asymmetric sense is in accord with the transition-state models of assemblies including a catalyst, dialkylzinc and aldehyde.[11] Thus, in the presence of (*S*)-amino alcohols as catalysts, the major configuration of the chiral secondary carbinols obtained is *R*, whereas the DBNE catalyst gives *S*-isomer as the main product.[13] Therefore, in this work we used two catalysts (AB and DBNE) to obtain the heterocyclic alcohols with the predominance either of *R*- or *S*-configuration, respectively.

The addition of Et_2Zn to 2-furaldehyde was investigated in the presence of AB (8 mol%) and DBNE (6 mol%). These reactions gave 1-(2-furyl)-1-propanol (**2**) in 83% and 96% yields (GC), respectively (Table 1, entries 3 and 4). In contrast to

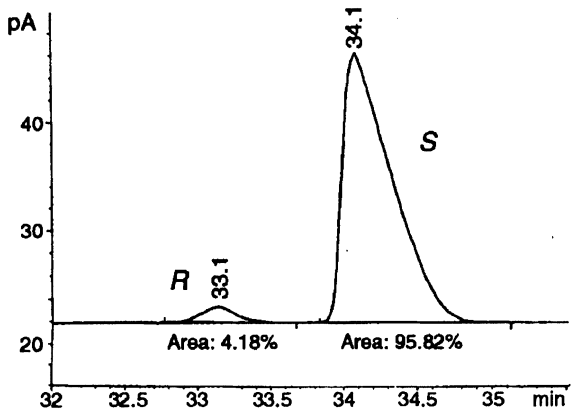


Figure 1 The GC chiral separation of 1-(2-thienyl)-1-propanol, prepared under DBNE catalysis (for other reaction conditions, see Table 1, entry 6). Column: chiral-phase Cyclodex IP (50 m × 0.2 mm), 120 °C.

alcohol **1**, the chiral resolution of **2** was impossible by means of the Cyclodex IP phase. The separation was successful on a Lipodex E column (25 m) at 85 °C. The *ee* values for the alcohol **2** were 36% (*R*) and 86% (*S*) under AB and DBNE catalysis, respectively. The result obtained with DBNE is comparable with that described by others[15,17] (89% *ee*, *S*-configuration).

1-(2-Thienyl)-1-propanol (**3**) was synthesized by the reaction of 2-thiophenecarbaldehyde with Et_2Zn (Table 1, entries 5 and 6) in moderate yield (55%) and in 38% *ee* (*R*-isomer) using AB catalyst (8 mol%) and in high chemical yield (98%, GC) and in 92% *ee* (*S*-configuration) in the presence of DBNE (6 mol%). The GC chiral resolutions of alcohol **3** were performed on chiral-phase Cyclodex IP (50 m) at 120 °C (Fig. 1). Optically active alcohol **3** has been prepared for the first time using asymmetric catalysis.

To our knowledge, the catalytic asymmetric synthesis of pyridylalkyl carbinol by enantioselective alkylation of pyridinecarboxaldehyde has been reported in only one paper.[16] 1-(3-Pyridyl)-1-propanol (**5**) was obtained in yield 93% (37% *ee*; configuration not reported yet) by the reaction of 3-pyridinecarbaldehyde with Et_2Zn (2.6 equiv) in hexane at 20 °C for 1 h in the presence of DBNE (5 mol%). In the presence of 75 mol% of DBNE the alcohol **5** was prepared in 99% yield and in 74% *ee*.

In the present work the asymmetric alkylation of 2-, 3- and 4-pyridinecarbaldehyde by Et_2Zn (2.2–2.7 equiv) was studied in the presence of chiral catalysts AB and DBNE (in various amounts) at 0 °C. 1-(2-Pyridyl)-1-propanol (**4**) was synthesized by the reaction of the corresponding aldehyde in up to 95% yield (in the presence of 6 mol% DBNE), but with very low enantioselectivity, i.e. 2% *ee* (and similarly under catalysis with 72 mol% DBNE; Table 1, entries 7 and 8). The GC chiral separation of alcohol **4** was performed on a column packed with chiral phase Lipodex E at 120 °C.

Alkylation of 3-pyridinecarbaldehyde was studied in the presence of AB (20 mol%) and DBNE (6, 40 and 68 mol%), and carbinol **5** was prepared (Table 1, entries 9–12). Chiral separation of enantiomeric **5** was successful only on the chiral phase Chirasil-Dex CB (Table 2). AB catalysed the reaction only with low enantioselectivity (11% *ee*). Under DBNE catalysis the *ee* values of **5** increased from 32 to 73% with an increase in the molar ratio of the catalyst and aldehyde from 6 to 68% (Fig. 2). These results are in agreement with those reported earlier.[16]

The reactions of 4-pyridinecarbaldehyde with diethylzinc were studied in the presence of AB (38 mol%) and DBNE (14.4–100 mol%) and the corresponding alcohol 1-(4-pyridyl)-1-propanol (**6**) was obtained. AB induced very low enantioselectivity — only 2.5% *ee*. The carbinol **6** was prepared by catalysis with DBNE in 96–100% yield

Table 2 GC chiral resolution of the prepared enantiomeric secondary (hetero)aromatic alcohols Ar-CH(OH)Et

				Configuration	
				R	*S*
Ar	Chiral GC phase	Length of capillary column (m)	Temp. (isothermal regime, °C)	Retention time (min)	
Ph	Cyclodex IP	50	120	30.2–30.4	31.1–31.3
Fur	Lipodex E	25	85	15.4–15.6	14.6–15.1
Th	Cyclodex IP	50	120	33.0–33.1	34.0–34.2
2-Py	Lipodex E	25	120	9.7–9.8	10.1–10.2
3-Py	Chirasil-Dex CB	25	140	13.8–14.0	14.2–14.4
			120	23.6	24.4
4-Py	Lipodex E	25	130	26.1–26.7	27.2–27.7
	Chirasil-Dex CB	25	130	21.8	24.0

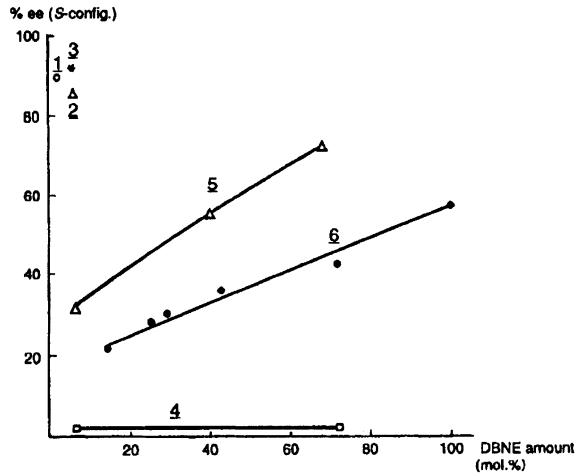


Figure 2 Dependence of the *ee* values on catalyst amount in the enantioselective syntheses of optically active alcohols (**1–6**) by asymmetric addition of Et_2Zn to aldehydes in the presence of (1*S*,2*R*)-*N*,*N*-dibutylnorephedrine (DBNE).

and with 22–57.5% *ee* stereoselectivity (Table 1, entries 13–19). As in the case of 3-pyridinecarbaldehyde, the increase in the amount of the catalyst leads to the enhancement of the *ee* (Fig. 2). The GC chiral resolutions of alcohol **6** were performed on two phases: Lipodex E and Chirasil-Dex CB, and identical results were obtained (Table 1, entry 15). As expected, GC analysis showed that alcohols **1–6** had opposite absolute configuration when obtained in the presence of AB compared with DBNE. The mass-spectral data of the prepared heterocyclic alcohols are presented in Table 3.

CONCLUSIONS

The enantioselective addition of diethylzinc to (hetero)aromatic aldehydes has been studied in the presence two amino alcohols, AB and DBNE. Six chiral alcohols were synthesized in high yields (95–98%, GC) and in moderate to high enantiomeric excess (up to 92%, *S*-configuration) in the presence of DBNE. Thienyl and 4-pyridyl derivatives (**3** and **6**) were obtained for the first time by catalytic asymmetric alkylation. The enantioselectivities of the AB catalyst were lower in all cases than those of DBNE. Different GC chiral phases have been found to be effective for the separation of the preparated chiral alcohols **1–6**. Some features of the asymmetric alkylation of heterocyclic aldehydes with Et_2Zn were found by studying the influence of the amount of DBNE on the *ee* values. In contrast to benzaldehyde, 2-furan- and 2-thiophene-carbaldehydes, in the cases of 3- and 4-pyridinecarbaldehydes an increase in the amount of catalyst leads to an enhancement of the enantioselectivity. The furan ring oxygen and the thiophene sulphur atoms seems to have only minor stereochemical consequences as potential sites of additional complexation, since the results obtained with 2-furan- and 2-thiophene-carbaldehydes are comparable with those obtained with benzaldehyde.

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Table 3 Mass-spectral data of the synthesized heterocyclic alcohols Het-CH(OH)Et: *m/z* (relative intensities, %)

Het	M^+	M^+-OH	M^+-Et	Het-CO^+	Het-C^+	(Het-H + H^+)	Het-H^+	Het^+
Fur	126 (17)	—	97 (100)	95 (6)	79 (4)	69 (19)	—	—
Th	142 (10)	—	113 (100)	111 (8)	95 (3)	85 (20)	—	83 (18)
2-Py	137 (2)	120 (13)	108 (100)	106 (17)	—	80 (18)	79 (20)	78 (35)
3-Py	137 (11)	—	108 (100)	106 (7)	—	80 (31)	—	78 (12)
4-Py	137 (23)	—	108 (100)	106 (7)	—	80 (48)	—	78 (10)

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