Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 1, pp. 67-72, 1994

0957-4166/94 $6.00+0.00

0957-4166(93)E0045-X

ENANTIOSELECTIVE ETHYLATION OF ALDEHYDES CATALYZED BY CHIRAL C_2-SYMMETRICAL β-HYDROXY-m-XYLYLENE DIAMINES

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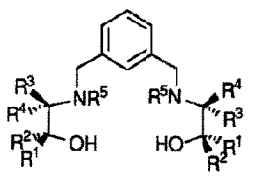
Abstract: Optically active C_2-symmetric aminoalcohols derived from m-xylylene diamine act as catalysts in enantioselective alkylation of aromatic and aliphatic aldehydes with diethylzinc. The chemical yields are good, and the enantiomeric excesses vary from moderate to excellent depending on both the aldehyde and the catalyst.

Since the first reports on the enantioselective alkylation of aldehydes by diethylzinc catalyzed by aminoalcohols[1,2] considerable work has been undertaken, to establish the mechanism and the stereochemical outcome of the reaction.[3-5] Considerable attention has also focused on the improvement of the chiral catalyst properties, having different structures and functionalities; in this respect, alkaloids,[6] diamines,[7] diols,[8] pyrrolidines,[9] piperazines,[10] organometallics,[11] ammonium salts,[12] hydroxyamines[13] and pyridine derivatives[14] among others[15] have been used as efficient catalysts for the enantioselective alkylation of aldehydes.

In this account we report on the enantioselective ethylation of aldehydes with diethylzinc using the chiral C_2-symmetric aminoalcohols **1A-I**[16] derived from m-xylylenediamine. Initially we tested reactions to see the modifications in both the chemical yield and enantiomeric excess depending on the experimental



1A-I

	R^1	R^2	R^3	R^4	R^5
1A	Ph	H	Me	H	Me
1B	Ph	H	Me	H	Et
1C	Ph	H	Me	H	Bn
ent-**1C**	H	Ph	H	Me	Bn
1D	Ph	H	Ph	H	Me
1E	Me	Me	Ph	H	Me
1F	Me	Me	Ph	H	Et
1G	Me	Me	H	i-Bu	Me
1H	Me	Me	H	i-Bu	Et
1I	Ph	Ph	H	i-Bu	Me

conditions. To this end, we have used the (+)-ephedrine-derived (+)-(1R,2S)-bis[N-methyl-N-(2-hydroxy-2-phenyl-1-methyl)-ethyl]-m-xylylenediamine (**1A**) as the test catalyst for comparative purposes, and the results are collected in Table 1.

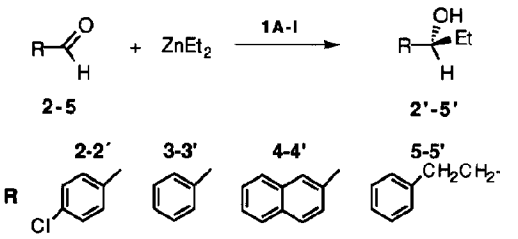


Table 1. Enantioselective addition of diethylzinc to aldehydes catalyzed by **1A**.

Entry	Aldehyde	Solvent[a]	Reaction Temp.(°C)	Reaction Time (h)	Molar ratio $ZnEt_2$/aldehyde	Catalyst mol-%	Yield(%)[b]	o.p.(%)[c] (e.e.)[d]
1	**2**	Hex./Tol.	20	24	1.1	10	**2'** (58)	71
2	**2**	Hex./Tol.	20	60	1.1	10	**2'** (82)	72
3	**2**	Hex./Tol.	20	60	2	5	**2'** (85)	44
4	**2**	Hex./Tol.	20	20	2	10	**2'** (95)	78
5	**2**	Hex./Tol.	20	6	2	15	**2'** (90)	75
6	**2**	Hex./Tol.	0	24	2	10	**2'** (88)	76
7	**2**	Hex./Tol.	60	1	2	10	**2'** (87)	70
8	**2**	Hex./Et_2O	20	20	2	10	**2'** (79)	68
9	**2**	Hex./Tol.	20	28	2	50	**2'** (63)	74
10	**3**	Hex./Tol.	20	6	2	10	**3'** (72)	80
11	**3**	Toluene	110	1.5	2	10	**3'** (60)	70
12	**3**	Hex./Tol.	20	6	2	15	**3'** (69)	78
13	**4**	Hex./Tol.	20	20	2	10	**4'** (84)	87 (86)
14	**4**	Toluene	110	1.5	2	10	**4'** (75)	84

[a]The ratio Hexane/Toluene was 1/2 (v/v). [b]The yields are referred to pure alcohol after column chromatography. [c]Determined by polarimetry based on the maximum values described for the optical rotations; the major enantiomers have S configuration. [d]Based on ^{1}H-NMR spectra of MTPA esters.

From these data, it can be deduced that the best results for 4-chlorobenzaldehyde (**2**) were achieved in the reaction with 2 eq. of 1M diethyl zinc in hexane at 20°C for 20 h and 10 mol-% of catalyst (Table 1, entry 4); in

these conditions alcohol (S)-**2'** was obtained with excellent chemical yield (95%) and good enantiomeric excess (78%). Moreover, 2-naphthaldehyde (**4**) was converted into (S)-**4'** (entry 13) in 80% chemical yield and 84% e.e.; whereas benzaldehyde (**3**) was transformed into (S)-**3'** in 72% chemical yield and 80% e.e. (entry 10) after stirring for 6 h with 2 eq. of diethyl zinc at 20°C.

In contrast, the reaction of 4-chlorobenzaldehyde with 1.1 eq. of diethyl zinc had not finished after stirring for 24 h in the presence of 10 mol-% of **1A** (entry 1), but hydrolysis with a 10% solution of hydrochloric acid, and column chromatography allowed the isolation of (S)-1-(p-chlorophenyl)propanol (S)-**2'** in 58% chemical yield and 71% e.e.; the reaction was completed after stirring for 60 h (entry 2) and the alcohol was isolated in 82% chemical yield and practically the same e.e. (72%).

The use of 10 mol-% of catalyst seems to be crucial for obtaining good enantioselectivity; in the presence of only 5 mol-% of the catalyst (entry 3) the alkylation was completed after a prolonged reaction time (60 h), and **2'** was isolated in good chemical yield (85%) but the e.e. dropped to only 44%, probably as a consequence of the competing catalytic alkoxides formed in these conditions.[17]

Instead, increasing the amount of **1A** to 15 mol-% showed only slight influence on both the chemical yield and the e.e. (compare entries 5 versus 4, and 12 versus 10 in Table 1), but in the reaction where a 50 mol-% of catalyst was used (entry 9) the chemical yield decreased to 63% and the e.e. to 74%.

When the reaction of 4-chlorobenzaldehyde was carried out in a mixture of solvents with donor properties (Hexane/diethyl ether: 1/2) (entry 8), both the chemical yield and the enantioselectivity decreased.[18]

The effect of the temperature was studied in the reactions of (**2**) (entries 6 and 7), (**3**) (entry 11) and (**4**) (entry 14). In the reaction of 4-chlorobenzaldehyde at 0°C a slight lowering in the e.e. was observed, whereas at 60°C, the alkylation had finished after heating for 1 h, but the e.e. decreased to 70%. At higher temperature (reflux of toluene) the alkylation of benzaldehyde (**3**) and 2-naphthaldehyde (**4**) occurred after 1.5 h; (S)-1-phenyl propan-1-ol (**3'**) and (S)-1-(2-naphthyl)propan-1-ol (**4'**) were isolated in lower chemical yields and e.e. than that in the reactions at room temperature. In these cases, it could be observed the formation of the reduction products, benzyl alcohol and 2-naphthyl methanol.

We turned our attention to the reactivity of aromatic aldehydes(**2-4**) and 2-phenylacetaldehyde (**5**) towards diethylzinc in the presence of different catalysts (**1A-I**). We examined the alkylation of the aldehydes, dissolved in toluene, with 2 equivalents of a solution of diethylzinc in hexane, at room temperature, and stirred until the disappearance of the aldehyde (shown by TLC). The results of these experiments are collected in Table 2.

It has been described previously that the alkyl substituents on the nitrogen atom in the catalysts derived from ephedrines and norephedrines play an important role in the enantioselectivity of the alkylation with diethylzinc.[4,19,20] In our case we tested the efficiency in the enantioselectivity of catalysts that differ only in the substituent on the nitrogen by comparing the e.e. obtained in the reactions catalyzed by the (1S,2R)-ephedrine-derived **1A**, and the N-ethyl- and N-benzyl-derivatives of (1S,2R)-norephedrine **1B** and **1C** respectively.

In fact, the N-ethyl derivative **1B** yielded a much better e.e. (10-17%) than did **1A** (compare entries 1, 10 and 15 in Table 2 versus 4, 10 and 13 in Table 1, or entries 21 versus 22 in Table 2); but the e.e., when N-benzylated catalysts **1C** or *ent*-**1C** were used, dropped to the same level than that obtained with **1A** (entries 2 and 3 versus 1 in Table 2). The same enhancement in the enantioselectivity, but to a lesser extent (4-5%), was systematically observed in the reactions with N-methyl- (**1E**) and N-ethylphenylglycinol (**1F**) derivatives as catalysts (entries 5, 11 and 17 versus 6, 12 and 18 in Table 2).

Table 2. Enantioselective Ethylation of Aldehydes **2-5** catalyzed by **1A-I**

Entry	Aldehyde	Catalyst	Alcohol	Yield (%)	e.e. (%)	Config.
1	**2**	**1B**	**2'**	82	95	S
2	**2**	**1C**	**2'**	80	78	S
3	**2**	*ent*-**1C**	*ent*-**2'**	82	78	R
4	**2**	**1D**	**2'**	85	75	S
5	**2**	**1E**	**2'**	75	75	S
6	**2**	**1F**	**2'**	84	79	S
7	**2**	**1G**	*ent*-**2'**	81	98	R
8	**2**	**1H**	*ent*-**2'**	87	91	R
9	**2**	**1I**	*ent*-**2'**	82	87	R
10	**3**	**1B**	**3'**	85	93	S
11	**3**	**1E**	**3'**	60	64	S
12	**3**	**1F**	**3'**	80	69	S
13	**3**	**1G**	*ent*-**3'**	83	90	R
14	**3**	**1H**	*ent*-**3'**	84	96	R
15	**4**	**1B**	**4'**	85	94	S
16	**4**	**1D**	**4'**	90	90	S
17	**4**	**1E**	**4'**	85	87	S
18	**4**	**1F**	**4'**	89	92	S
19	**4**	**1G**	*ent*-**4'**	93	94	R
20	**4**	**1H**	*ent*-**4'**	87	93	R
21	**5**	**1A**	**5'**	50	51	S
22	**5**	**1B**	**5'**	56	79	S
23	**5**	**1D**	**5'**	20	58	S
24	**5**	**1G**	*ent*-**5'**	59	64	R
25	**5**	**1H**	*ent*-**5'**	55	71	R

However, this effect is quite erratic in the processes catalyzed by (S)-leucine derivatives; thus, N-ethyl derivative **1H** leaded to better e.e. than N-ethylated compound **1G** in the alkylations of benzaldehyde and 2-phenylacetaldehyde (entries 14 and 25 versus 13 and 24 in Table 2), whereas the contrary effect was found in the reactions of 4-chlorobenzaldehyde (entry 7 versus 8 in Table 2), and a negligible change was produced in the additions to 2-naphthaldehyde (entries 19 and 20 in Table 2).

The results obtained by using the catalyst **1D**, derived from (1S,2R)-2-amino-1,2-diphenylethanol, were quite similar to those obtained in the reactions of ephedrine derivative **1A**, and the substitution of the *gem*-methyl groups attached to the alcohol part in **1G**, by phenyl substituents in **1I** did not improve the e.e. in the ethylation of 4-chlorobenzaldehyde (entry 9 versus 7 in Table 2).

The sense of the asymmetric induction can be rationalized taking into account the previously proposed transition state models.[5, 21] The stereochemistry of the major enantiomer depends on the configuration of the stereocenters at the catalysts; thus, in the reactions where the catalysts are S-configurated at C-OH and R at C-N (**1A-D**) the alkylation is produced from the *si*-face of the aldehyde, giving the S enantiomer of the alcohols; obviously, catalyst *ent*-**1C** leads preferentially to the R enantiomer.

Catalysts with only one stereogenic center at C-N also promote the enantioselective alkylation.[22] In this case the configuration of the stereocenter of the alkylation products is just the opposite to that present in the catalyst; (1R,1'R)-**1E** and (1R,1'R)-**1F**, derived from (R)-phenylglycine, yield the S-enantiomer of the alcohols; whereas (1S,1'S)-**1G-I**, prepared from (S)-leucine, direct the alkylation from the *re*-face of the aldehyde, and lead to the R-configured alcohol.

In summary, C_2-symmetric chiral aminoalcohols **1A-I** are effective catalysts for the enantioselective alkylations of aldehydes with diethylzinc. In general, all of them gave good chemical yields and e.e., and the best results are obtained by using the N-ethylnorephedrine derivative **1B** and leucine-derived **1G** and **1H**. The rationalization of the stereochemistry in the final alcohols is consistent with the previously proposed models for related enantioselective additions.

EXPERIMENTAL.

General. The reactions were carried out in oven-dried glassware, under argon atmosphere, and using anhydrous solvents. Aldehydes, commercially available, were distilled prior to use. Diethylzinc, as 1M solution in hexane or 1.1M solution in toluene, was purchased from Aldrich, and used without further purification. The ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra were registered on a Bruker AC 300, using TMS as internal standard. IR spectra were recorded on a Philips PU 9706 Spectrometer, as film or KBr dispersion. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter in a 1 dm. cell. Products were isolated by column chromatography (silica gel, hexane/ethyl acetate: 5/1), and purified by bulb-to-bulb distillation (1-(4-chlorophenylpropan-1-ol and 1-phenylpropan-1-ol) or by recrystallization for 1-(2-naphthyl)propan-1-ol (m.p. 50-51ºC, from hexane/ethyl acetate) and 1-phenylpentan-3-ol (m.p. 37-38ºC, from hexane).

General method of alkylation. An 25 ml oven-dried flask equipped with a septum and a magnetic stirrer and purged with argon, was charged with the corresponding aldehyde (2 mmol), catalyst (0.2 mmol), and 8 ml of anhydrous toluene. The solution was cooled to 0ºC (ice bath), and 4 ml of 1M solution of diethylzinc in hexane (4 mmol., 2 equivalents) were injected through the septum, and the mixture was allow to rise to room temperature. The mixture was stirred at that temperature until the reaction was finished (TLC), and then quenched with 8 ml. of a 10% solution of hydrochloric acid. The organic layer was separated and the aqueous phase was extracted with diethyl ether (3x 20 ml). The combined organic layers were washed with brine, and dried over anhydrous Na_2SO_4. The solvents were eliminated on Rotavapor and the residue purified by column chromatography. The e.e. were determined by comparison of the specific rotations with the maximum values previously described: (S)-1-(4-chlorophenyl)propan-1-ol (**2'**): $[\alpha]_D^{22}$= -28.2 (c 5.01, C_6H_6).[23] (S)-1-phenylpropan-1-ol (**3'**): $[\alpha]_D^{22}$= -47.6 (c 6.11, $CHCl_3$).[4] (S)-1-(2-naphthyl)propan-1-ol (**4'**): $[\alpha]_D^{22}$= -26.6 (c 3.35, C_6H_6).[23] (S)-1-phenylpentan-3-ol (**5'**): $[\alpha]_D^{22}$= +26.8 (c 5.0, EtOH).[24] Mosher's derivatives[25] for compounds **2'** and **3'** have been previously published.[18] The e.e. for alcohol **4'** was determined by integration of the OCH_3 signals in ^{1}H-NMR spectra of the diastereomeric mixtures of ester derived from (R)-(-)-MTPA

chloride.[26] The signal of methoxy group for the ester of (R)-**4'** appeared, as a quartet (J= 1.27 Hz), at 3.44 ppm, and for the ester of (S)-**4'** at 3.55 (ratio for the experience 13, in Table 1: 7/93).

ACKNOWLEDGEMENTS

We thank the Spanish DGICYT for the financial support of this work (Project PB89-0356). One of us (M.A.M.) thanks to the Universidad de Valladolid for a predoctoral fellowship.

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(*Received in UK* 12 *October* 1993)