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Asymmetric Ethylation of Aromatic Aldehydes by Diethylzinc in the Presence of Chiral Auxiliaries Derived from (*S*)-[4-$HOC_6H_4CH_2CH(NH_2)CPh_2OH$]

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A comparative study has been carried out on enantioselective ethylation of aromatic aldehydes (ArCHO) by diethylzinc (Et_2Zn) in the presence of catalytic amounts of (*S*)-[4-$HOC_6H_4CH_2CH(NH_2)CPh_2OH$] (1) or chiral auxiliaries derived from (1). Various procedures have been adopted; these involved (i) different sequences of addition of the reagents ArCHO, Et_2Zn and (1), and (ii) use of titanium(IV)isopropoxide [$Ti(OPr^i)_4$] or the borane–tetrahydrofuran addition compound ($BH_3 \cdot THF$) as additional reagents. In all but one of the procedures adopted, (*S*)-ArCH(OH)Et was selectively formed; enantiomeric excess values up to 87% were obtained.

Keywords: asymmetric synthesis; enantioselective ethylation; aldehydes; metal complexes; organozinc; boron

INTRODUCTION

Enantioselective alkylation of aldehydes by dialkylzinc compounds can occur in the presence of chiral auxiliaries,[1–7] (Eqn [1]). Dialkylzinc compounds are generally unreactive towards aldehydes in hydrocarbon or ethereal solvents at ambient temperature. The lack of reactivity is a consequence of the alkyl–zinc bonds in linear dialkylzinc species being insufficiently polar. The polarity (and hence reactivity) of an alkyl–zinc bond is greater in compounds having non-linear geometries at zinc. Both aprotic (L) and protic (R″OH) additives can act as promoters of R_2Zn by formation of higher-coordinate zinc species, $[R_2Zn(L)_n]$ and $[(RZnOR'')_n]$. If the additive is chiral, then a chiral alkylating agent can be generated. Particularly effective chiral additives are β-aminoalcohols, such as *N*,*N*-dialkylnorephedrines,[2] *N*-alkylephedrines,[3] cinchona alkaloids[4] and 3-(dialkylamino)isoborneols.[5] Large enantiomeric excess values and high catalytic turnovers have been realized with such additives. A number of different procedures for enantioselective alkylation have been employed; among these are methods which also utilize titanium[8] and boron[9] co-reagents.

$$RCHO \xrightarrow[\text{(ii) } H_2O]{\text{(i) } R'_2Zn/L \text{ or } R''OH} RR'CHOH \qquad [1]$$

We report here a comparative study of the enantioselective ethylation of substituted benzaldehydes by Et_2Zn, in the presence of chiral auxiliaries derived from (*S*)-[4-$HOC_6H_4CH_2CH(NH_2)CPh_2OH$] (1).

EXPERIMENTAL

NMR spectra were produced on a Bruker 250 MHz spectrometer. IR spectra were obtained using a Philips PU 9800 series FTIR spectrometer. Mass spectra were recorded by the SERC mass spectrometry service, based at Swansea.

Procedures

All reactions with organozinc and organomagnesium compounds were carried out under nitrogen. Solvents were dried and purified by standard means.

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Compounds

(*S*)-Tyrosine methyl ester hydrochloride, (S)-[4-$HOC_6H_4CH_2CH(CO_2Me)NH_3^+,Cl^-$], (*R*)-(+)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid, diethylzinc and the borane–tetrahydrofuran complex ($BH_3 \cdot THF$) were commercial samples.

Preparation of (*S*)-2-amino-3-(4-hydroxyphenyl)-1,1-diphenylpropanol (1)

(*S*)-4-$HOC_6H_4CH_2CH(CO_2Me)NH_3^+,Cl^-$ (25.48 g, 0.110 mmol) was added in portions to an ice-cold THF solution of phenylmagnesium bromide, obtained from PhBr (80.78 g, 0.515 mmol) and magnesium (13.08 g, 0.538 mmol) in 200 ml tetrahydrofuran (THF). After the addition was complete, the reaction mixture was stirred at 0 °C for 5 h and then hydrolysed with an aqueous solution of ammonium chloride (NH_4Cl). The organic layer was collected and the aqueous layer was extracted with ethyl acetate (EtOAc) four times. The combined organic extracts were dried over magnesium sulphate ($MgSO_4$) and evaporated to leave a pale yellow residue. This was recrystallized from EtoH/EtOAc/H_2O (3:1:2) to give colourless crystals of (**1**); yield, 13.59 g (38.7%); m.p. 212–215 °C (lit.[10] m.p. 215–217 °C).

Asymmetric alkylation of aromatic aldehydes

Methods A–E were used.

Method A

A solution of the aromatic aldehyde (15 mmol) and (**1**) (0.16 g, 0.5 mmol) in toluene (30 ml) was maintained at room temperature (RT) for 15 h. After cooling to 0 °C, a solution of Et_2Zn (30.0 ml of a 1.0 m solution in hexane) was added and the reaction mixture was stirred for 24 h at 0 °C and then hydrolysed using 2 M HCl solution. The organic layer was collected, washed with aqueous sodium carbonate (Na_2CO_3) and rotary-evaporated. The alcohol product was purified using a chromatotron, with hexane/EtOAc as the eluent.

Method B

A solution of Et_2Zn (30 ml of a 1 M solution in hexane) was added to a solution of (**1**) (0.16 g, 0.5 mmol) in toluene (30 ml) at 0 °C. After being stirred for 15 min, the solution was cooled to −78 °C and the aromatic aldehyde added. The reaction mixture was allowed to warm to 0 °C and after 24 h was quenched, and worked up as described in Method A.

Method C

A mixture of $Ti(OPr^i)_4$ (7.40 g, 26 mmol) and (**1**) (0.16 g, 0.5 mmol) in toluene was stirred at 80 °C for 45 min. After being cooled to −78 °C, a solution of Et_2Zn (28 ml of a 1.0 M solution in hexane) and an aldehyde (26 mmol) were successively added. The reaction mixture was warmed to −40 °C, stirred for 3 h, and worked up as described in Method A.

Method D

A solution of (**1**) (0.30 g, 0.9 mmol) and the aldehyde (14 mmol) in toluene (30 ml) was stirred at RT for 15 h. After addition of $Ti(OPr^i)_4$ (0.40 g, 1 mmol), the reaction mixture was stirred at RT for 2 h, cooled to −78 °C, and a solution of Et_2Zn (150 ml of a 1.0 M solution in hexane) added. The reaction mixture was kept at −40 °C for 24 h, and worked up as described in Method A.

Method E

A mixture of (**1**) (0.31 g, 1 mmol) and $BF_3 \cdot THF$ (2.0 mmol) in THF (50 ml) was stirred initially at RT for 1 h and then at 60 °C for 15 h. The volatiles were removed under vacuum at 40 °C, then toluene (30 ml) and an aldehyde (1.14 mmol) were successively added. After cooling to 0 °C, a solution of Et_2Zn (15 ml of a 1.0 M solution in hexane) was added. The reaction mixture was maintained at 0 °C for 48 h and was then worked up as in Method A.

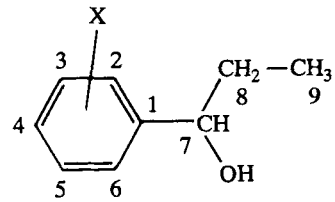
1-Aryl-1-propanol products

The pure enantiomeric mixtures of the 1-aryl-1-propanols were obtained as oils after chromatography. Chemical analyses and ^1H NMR spectra for ArCH(OH)Et were as expected; the parent peaks were observed in the EI mass spectra. The ^{13}C NMR spectra are shown in Table 1.

Preparation of 1-arylpropyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoates

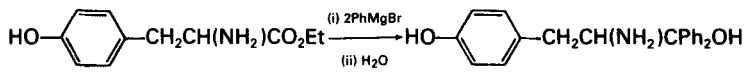
A mixture of a 1-aryl-1-propanol, ArCH(OH)Et (0.10 mmol) and (*R*)-$PhC(CF_3)(OMe)COCl$ (93.8 mg, 6.4×10^{-5} l), obtained by a published

Table 1 ^{13}C NMR spectra of ArCH(OH)Et in $CDCl_3$

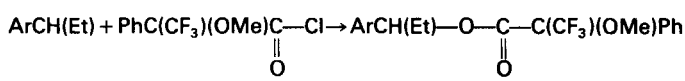


	$\delta^{13}C$									
X	C1	C2	C3	C4	C5	C6	C7	C8	C9	Other
H[a]	144.6	126.0	128.2	127.2	128.2	126.0	75.7	31.7	10.1	
H	144.8	126.5	128.4	127.4	128.4	126.5	75.9	31.9	10.3	
4-Me	141.9	129.1	129.1	136.9	129.1	129.1	75.8	31.9	10.3	21.2 (Me)
4-Cl	143.1	127.4	128.4	133.1	128.4	127.4	75.2	31.9	9.9	
4-MeO	136.9	127.3	113.7	158.8	113.7	127.3	76.7	31.8	10.3	55.2 (OMe)
2-Cl	141.8	131.7	128.1	126.7[b]	126.9[b]	128.9	71.4	30.3	9.7	
2-Br	143.5	122.0	132.4	128.8	127.3[c]	127.5[c]	73.9	30.4	10.0	
2-MeO	132.3	156.4	110.3	127.9	120.5	127.9	71.9	30.0	10.3	55.1 (OMe)

[a] Ref. 13. [b] Could be interchanged. [c] Could be interchanged.



(1) [2]

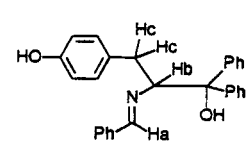


[3]

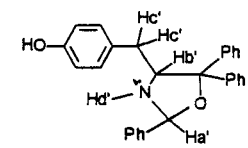
procedure from the corresponding acid,[11] was stirred at RT for 24 h. Excess $Me_2NCH_2CH_2CH_2NH_2$ (50 mmol) was added, and the reaction mixture was diluted with Et_2O, washed successively with dilute HCl, Na_2CO_3 and water, dried over $MgSO_4$, and then evaporated. The ^1H NMR spectrum of the residue was obtained to determine the proportions of the (*R*,*S*)- and (*R*,*R*)-$PhC(CF_3)(OMe)CO_2CHArEt$ products. The ratio of diastereomers was calculated from the integration for the CH_3CH_2 protons; the (*R*, *S*) isomer has the lower ^1H (CH_3) value.

^1H NMR spectral investigation of the interaction of (1) and PhCHO

A mixture of PhCHO (0.006 g, 5.6×10^{-5} mol) and (1) (0.0015 g, 15×10^{-5} mol) in $CDCl_3$ was maintained at RT for 15 h. Products identified were the chiral Schiff's base (2) and the oxazolidene derivative (3).



(2)



(3)

^1H NMR ($CDCl_3$): 7.9–6.6 (m, phenyl). Compound (2): 5.53 (s, 1H, H_4), 4.35 (t, 1H, $J(^1H_c-^1H_b) = 6$ Hz, H_b), 2.79 (d, 2H, $J(^1H_c-^1H_b) = 6$ Hz, H_c), 2.70 (br.s, 1H, OH). Compound (3): 4.34 (d, 1H, $J(^1H_{a'}-^1H_{d'}) = 11$ Hz, $H_{a'}$), 2.79 (dd, 2H, $J(^1H_{c'}-^1H_{b'}) = 4$ Hz, $J(^1H_{c'}-^1H_{d'}) = 14$ Hz, $H_{c'}$), 2.67 (dd, 2H, $J(^1H_{b'}-^1H_{c'}) = 4$ Hz, $J(^1H_{b'}-^1H_{c'}) = 15$ Hz, $H_{b'}$), 1.88 (dd, 1H, $J(^1H_{a'}-^1H_{d'}) = 11$ Hz, $J(^1H_{b'}-^1H_{d'}) = 15$ Hz, $H_{d'}$).

Table 2 Sequences used in the ethylation of substituted benzaldehydes

Method	Addition sequence			
A	(i) (**1**)	(ii) Et_2Zn	(iii) ArCHO	
B	(i) (**1**)	(ii) ArCHO	(iii) Et_2Zn	
C	(i) (**1**)	(ii) $Ti(OPr^i)_4$	(iii) Et_2Zn	(iv) ArCHO
D	(i) (**1**)	(ii) ArCHO	(iii) $Ti(OPr^i)_4$	(iv) Et_2Zn
E	(i) (**1**)	(ii) $BH_3 \cdot THF$	(iii) ArCHO	(iv) Et_2Zn

RESULTS AND DISCUSSION

The chiral source used throughout this study was (**1**), prepared as shown in Eqn [2]. The different procedures employed to ethylate the aromatic aldehydes, ArCHO, are given in Table 2, with the results listed in Table 3. The chemical yields quoted in Table 3 are for purified products, obtained after chromatography. The enantiomeric excess (e.e.) values of the ArCH(OH)Et products were deduced from the ^1H NMR spectra of the ester derivatives,[11,12] ArCH(Et)OC(O)(CF_3)(OMe)Ph, obtained as shown in Eqn [3].

Table 3 Enantioselective ethylation of aromatic aldehydes using Et_2Zn in the presence of (**1**), or chiral auxiliaries derived from (**1**)

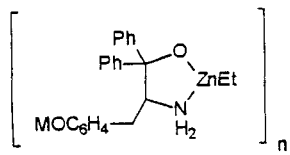
					Product, $XC_6H_4CH(OH)Et$		
Entry no.	Reagents, XC_6H_4CHO: X	Ratio ($[XC_6H_4CHO]:[Et_2Zn]:$**11**])	Additional reagent [concn (mmol)]	Method	Chemical yield (%)	Optical yield, e.e. (%)	Configuration
1	*p*-Me	15:30:0.25	—	A	73	46	*S*
2	*p*-Me	15:30:0.50	—	A	72	86	*S*
3	*p*-Me	15:30:1.0	—	A	74	83	*S*
4	*p*-Me	15:30:2.0	—	A	71	83	*S*
5	H	15:30:0.50	—	A	65	81	*S*
6	*p*-Cl	15:30:0.50	—	A	80	66	*S*
7	*p*-MeO	15:30:0.50	—	A	75	44	*S*
8	*o*-Cl	15:30:0.50	—	A	75	43	*S*
9	*o*-Br	15:30:0.50	—	A	85	64	*S*
10	*o*-Me	15:30:0.50	—	A	70	64	*S*
11	H	15:30:0.50	—	B	60	34	*S*
12	*p*-Me	15:30:0.50	—	B	70	37	*S*
13	*o*-Me	15:30:0.50	—	B	65	86	*S*
14	*o*-Cl	15:30:0.50	—	B	75	87	*S*
15	H	26:28:0:50	$Ti(OPr^i)_4$ [26]	C	32	27	*R*
16	*o*-Cl	26:28:0:50	$Ti(OPr^i)_4$ [26]	C	40	9	*R*
17	*p*-Me	26:28:0:50	$Ti(OPr^i)_4$ [26]	C	30	13	*R*
18	*o*-Me	26:28:0:50	$Ti(Opr^i)_4$ [26]	C	47	11	*R*
19	H	14:15:0.90	$Ti(OPr^i)_4$ [1.0]	D	30	47	*S*
20	*o*-Cl	14:15:0.90	$Ti(OPr^i)_4$ [1.0]	D	21	15	*S*
21	H	14:15:1.0	$BH_3 \cdot THF$ [2.0]	E	55	43	*S*
22	*o*-Cl	14:15:1.0	$BH_3 \cdot THF$ [2.0]	E	40	43	*S*
23	*p*-Me	14:15:1.0	$BH_3 \cdot THF$ [2.0]	E	59	78	*S*
24	*o*-MeO	14:15:1.0	$BH_3 \cdot THF$ [2.0]	E	62	84	*S*

The e.e. values are based on the ratios of $(S):[(S)+(R)]$ or $(R):[(S)+(R)]$ of the ArCH(OH)Et products.

Ethylations involving (1), Et_2Zn and ArCHO (Methods A and B)

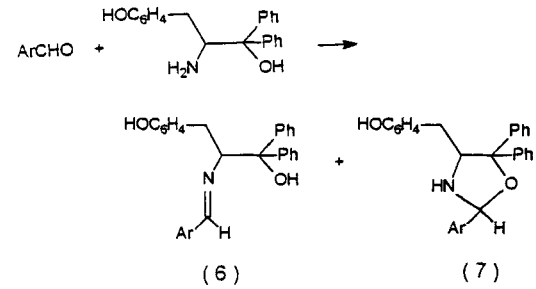
The successful use of (S)-$PhCH_2CH(NH_2)CPh_2OH$ (**4**) as a chiral auxiliary in the reaction of Et_2Zn with PhCHO has been reported by Itsuno *et al.*[6] These authors used the addition sequences that we term Methods A and B, i.e. (i) chiral auxiliary (**4**), (ii) Et_2Zn and (iii) aldehyde (Method A) and (i) chiral auxiliary, (ii) aldehyde and Et_2Zn (Method B). The dominant product, in both methods, was (S)-PhCH(OH)Et, with the higher e.e. values being obtained using Method B. Itsuno *et al.*'s study, however, only involved the single aldehyde, PhCHO. As shown in Table 3, entries 1–14, (**1**) can be sucessfully used a a chiral auxiliary with various aromatic aldehydes by either Method A or B. The major product in all cases was (S)-ArCH(OH)Et. Using Method A, the e.e. values for the (S)-ArCH(OH)Et products increased in the order $Ar = 4\text{-}MeOC_6H_4 < 4\text{-}ClC_6H_4 < C_6H_5 < 4\text{-}MeC_6H_4$ and $2\text{-}ClC_6H_4 < 2\text{-}BrC_6H_4 = 2\text{-}MeC_6H_4$. No correlations of the e.e. values with the electronic effects (for *para*-substituents) or with steric effects (for *ortho*-substituents) are evident. Generally, the mole ratios of reagents used were $[Et_2Zn]:[ArCHO]:[1] = 30:15:0.5$; smaller amounts of (**1**) led to poorer optical yields.

Although low e.e. values (<40%) were obtained using Method B with PhCHO and $4\text{-}MeC_6H_4CHO$, high e.e. values (>86%) were produced in reactions of the *ortho*-substituted aldehydes, $2\text{-}ClC_6H_4CHO$ and $2\text{-}MeC_6H_4CHO$. From the latter results, it can be argued that steric effects aid the selectivity in ethylations via Method (B). The addition sequence used in Method A will result in the initial formation of an enolate, such as (5), which is expected to form the template for the ethylations.

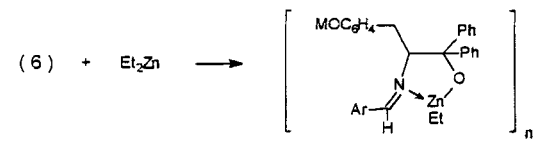


(5; M = H or EtZn)

The addition of ArCHO to (**1**), as used in Method B, was shown by ^1H NMR spectra to produce a mixture of a Schiff's base (**6**) and an oxazolidine (**7**) (Eqn [4]) In method B, the chiral Schiff's base is considered to be the effective chiral reagent. The Schiff's base (**6**) will generate a reactive ethylzinc enolate [e.g. (**8**)] on reaction with Et_2Zn (Eqn [5]). Similar deductions were made by Itsuno *et al.*[6]



(6) (7) [4]

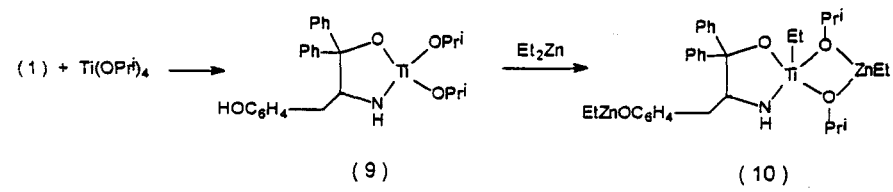


(8) [5]

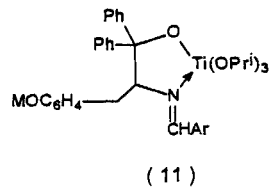
The phenolic hydroxy group in (**1**) is not expected to remain inert towards Et_2Zn (nor towards other metal compounds), but rather to form ethylzinc phenolate species. While the non-chiral ethylzinc phenolate site could be sufficiently reactive to take part in ethylation of ArCHO, the stereochemical results indicate that it cannot dominate the reactions.

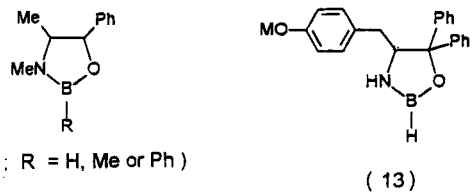
Reactions involving $Ti(OPr^i)_4$ as a co-reagent

Two procedures were adopted using $Ti(OPr^i)_4$ as an additional reagent, Methods C and D. Neither gave good results, in terms of either chemical or optical yields; see entries 15–20 in Table 3. The addition sequence used in Method C was (i) (**1**), (ii) $Ti(OPr^i)_4$, (iii) Et_2Zn and (iv) ArCHO. The initial reaction of $Ti(OPr^i)_4$ and (**1**) is considered to provide a titanium enolate, such as (**9**), which can subsequently react with Et_2Zn to give a mixed titanium/zinc species (**10**)) (Eqn [6]). The latter is considered to be the effective chiral reagent in the ethylation reactions. Yoshioka *et al.*[8] showed, by ^1H NMR spectroscopy, that Et_2Zn and $Ti(OPr^i)_4$ can take part in exchange reactions to form ethyltitanium species. The intermediacy of mixed titanium/zinc complexes have also been proposed



[6]





in reactions using sulphonamides as the chiral auxiliaries.[8] The addition sequence used in Method D was (i) (**1**), (ii) ArCHO, (iii) Ti (OPr^i)$_4$ and (iv) Et_2Zn. This should lead to the initial formation of the chiral Schiff's base (**6**), which would react further with Ti(OPr^i)$_4$ to give (**11**). Again as in Method C, a mixed ethyltitanium/ethylzinc species would be formed on reaction of (**11**) with Et_2Zn.

While (*R*)-ArCH(OH)Et dominated in Method C, the (*S*) enantiomer was the major product by Method D. Clearly the active ethylating agents in Methods C and D present different stereochemical situations for the aldehyde substrates.

Reactions involving $BH_3 \cdot THF$ as the co-reagent

Brown and co-workers[9] have used chiral 1,3,2-oxazaborolidine derivatives (**12**) as auxiliaries in enantiomeric alkylations of aldehydes. The 1,3,2-oxazaborolidines were generated *in situ* from ephedrine, MeNHCHMeCHPhOH and $BH_3 \cdot SMe_2$ or RB $(OR^1)_2$. High e.e. values (>95%) of (*R*)-ArCH(OH)Et were obtained from ArCHO, using (**12**; R = H) as the chiral auxiliary. An addition sequence of (i) (**1**), (ii) $BH_3 \cdot THF$, (iii) ArCHO and (iv) Et_2Zn (Method E) was used in this study. This sequence will lead to the formation of an oxazaborolidine (**13**), which will act as the active chiral ligand. The e.e. values of the (*S*)-ArCH(OH)Et products are mixed; see entries 21–24 in Table 3. Reasonably good e.e. values were obtained for the compounds containing the electron-releasing groups, 2-$MeOC_6H_4CH(OH)Et$ and 4-$MeC_6H_4CH(OH)Et$.

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