

Nonlinear Relationship between the Enantioselectivities for Asymmetric Reactions of Monofunctional and Bifunctional Substrates. Synthesis of Practically Optically Pure Diols by the Catalytic Enantioselective Diethylation of Terephthalaldehyde

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An equation is presented which shows a nonlinear relationship between the enantioselectivities for asymmetric reactions of bifunctional and monofunctional substrates; practically complete enantioselectivity (100% e.e.) was observed in the enantioselective diethylation of terephthalaldehyde with diethylzinc using *N,N*-di(*n*-butyl)norephedrine and (*S*)-diphenyl(1-methylpyrrolidin-2-yl)methanol as chiral catalysts.

Optically active bifunctional compounds possessing a C_2 symmetry axis form an important class of compounds, functioning as, *e.g.* chiral auxiliaries in asymmetric syntheses¹ and in chiral recognition.² One method for obtaining these optically active bifunctional compounds is *via* asymmetric synthesis starting from achiral symmetrical bifunctional compounds. For example, optically active diols possessing a C_2 symmetry axis have been synthesised by the enantioselective reduction of symmetrical diketones.³

When an enantioselective reaction is applied to an achiral symmetrical bifunctional compound, is the enantioselectivity of the reaction the same as that of the reaction of the

monofunctional compound? We here present equations defining the relationship of the enantioselectivities for the monofunctional substrate and the bifunctional substrate.

If the enantiomeric excesses (e.e.) of asymmetric reactions with monofunctional (single step) and bifunctional substrates (double step) are $x\%$ and $y\%$, respectively, the relationship between x and y is given by eqns. (1) and (2).[†] This may be

[†] These considerations apply when the second (double) step of the asymmetric reaction is not affected by the chiral centre formed in the first (single) step of the asymmetric reaction.

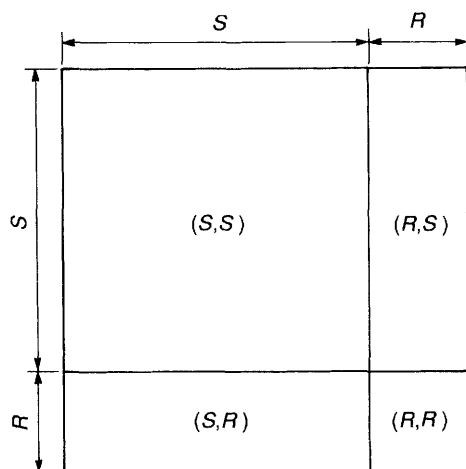
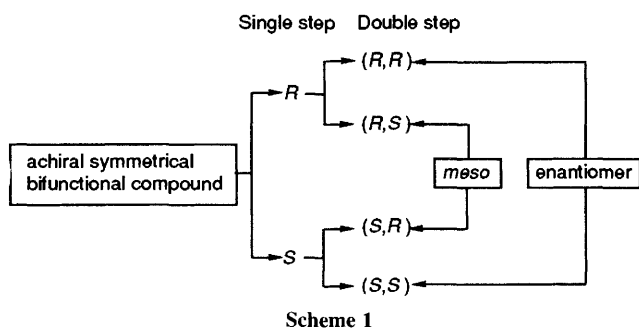


Fig. 1 Product distribution for the double-step reaction

proved as follows (see Scheme 1). The ratios of the selectivi-

$$y = 2 \times 10^4 x / (x^2 + 10^4) \quad (1)$$

$$x = [10^4 - 10^2 (10^4 - y^2)^{1/2}] / y \quad (2)$$

ties in the double-step reaction are the square of those in the single-step reaction, *i.e.* the area as shown in Fig. 1.

If the *S* enantiomer is predominant ($S > R$), $x\%$ e.e. (single step) is given by $100(S - R)/(S + R)$. $S + R = 100$, so eqns. (3)

$$\begin{aligned} S &= 50 + x/2 \\ R &= 50 - x/2 \end{aligned} \quad (3)$$

hold. Compounds (*S,S*) and (*R,R*) are enantiomers, so $y\%$ e.e. (double step) for the enantiomer (*S,S*) is given by eqn. (4). Eqn. (1) is obtained when eqn. (3) is substituted in eqn. (4).

$$y = 100 [(S,S) - (R,R)] / [(S,S) + (R,R)] = (S \times S - R \times R) / (S \times S + R \times R) \quad (4)$$

On the other hand, the percentage of *meso*-compound ($z\%$) in the total product [eqn. (6)] is given by substituting eqn. (3) in eqn. (5).

$$\begin{aligned} Z &= 100[(R,S) + (S,R)] / (100 \times 100) = (2 \times S \times R) / 100 \quad (5) \\ z &= 50 - x^2/200 \quad (6) \end{aligned}$$

The relationship between x and y is shown in Fig. 2. The same relationship and the product ratios are also shown in Table 1. As shown in Fig. 2, the e.e.s for bifunctional substrates are higher than those for the monofunctional compounds. When the e.e. x is only 50%, for example, y should be 80% [eqn. (1); Table 1]. On the other hand, to attain an e.e. y of 95%, an e.e. x of only 72.4% should be required [eqn. (2)].

The above considerations apply in the catalytic enantioselective diethylation of a dialdehyde. When terephthalaldehyde **1** was treated with diethylzinc in the presence of a catalytic amount of (1*S*,2*R*)-(-)-di(*n*-butyl)norephedrine (DBNE)⁴ in a mixed solvent of tetrahydrofuran (THF) and

Table 1 Relationship between enantioselectivities for single- and double-step reactions and product ratios

Enantiomeric excess (%)		Ratios of double step		
Single step, x	Double step, y	SS (%)	RR (%)	<i>meso</i> -SR (z) (%)
5.00	9.98	27.56	22.56	49.875
10.00	19.80	30.25	20.25	49.500
15.00	29.34	33.06	18.06	48.875
20.00	38.46	36.00	16.00	48.000
25.00	47.06	39.06	14.06	46.875
30.00	55.05	42.25	12.25	45.500
35.00	62.36	45.56	10.56	43.875
40.00	68.97	49.00	9.00	42.000
45.00	74.84	52.56	7.56	39.875
50.00	80.00	56.25	6.25	37.500
55.00	84.45	60.06	5.06	34.875
60.00	88.24	64.00	4.00	32.000
65.00	91.39	68.06	3.06	28.875
70.00	93.36	72.25	2.25	25.500
75.00	96.00	76.56	1.56	21.875
80.00	97.56	81.00	1.00	18.000
85.00	98.69	85.56	0.56	13.875
90.00	99.45	90.25	0.25	9.500
95.00	99.87	95.06	0.06	4.875
100.00	100.00	100.00	0.00	0.000

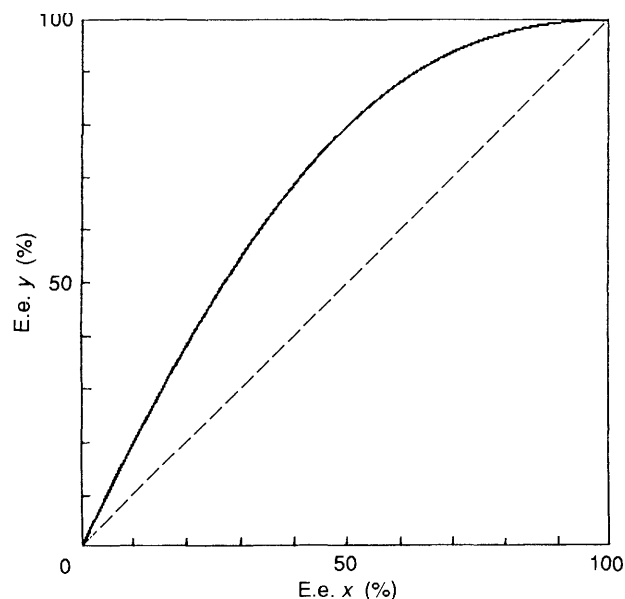
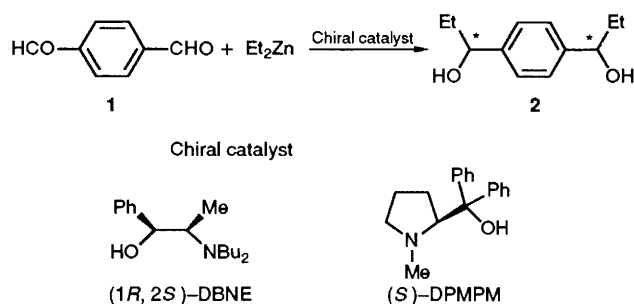


Fig. 2 Relationship between the enantiomeric excess for bifunctional (y) and monofunctional substrates (x) (solid line). (For comparison, the broken line shows $y = x$).

hexane at reflux for 40 min (molar ratio, **1** : Et₂Zn : DBNE = 1 : 4 : 0.2), 1,4-bis(1-hydroxypropyl)benzene **2** (optically active diol and *meso*-diol) was obtained in 74% yield (ratio of optically active **2** to *meso*-**2** = 80 : 20). The e.e. of the optically active **2** was found to be 100% by HPLC analysis using a chiral column.[‡] The reaction temperature did not affect the e.e. of **2**. When the same reaction was performed at room temperature for 26 h, **2** of 100% e.e. was again obtained (54% yield, ratio of optically active to *meso* = 84 : 16). The opposite enantiomer of **2** was obtained in 100% e.e. (62% yield) when (1*R*,2*S*)-(+)-DBNE was used. In addition, when (*S*)-(+)-diphenyl(1-

[‡] The minor enantiomer was not detected. Configuration is tentatively assigned as (*S,S*) based on the results for the formation of (*S*)-1-phenylpropanol from benzaldehyde and Et₂Zn in the presence of (1*S*,2*R*)-(-)-DBNE⁴ and (*S*)-DPMPM.⁵



methylpyrrolidin-2-yl)methanol (DPMPM)⁵ was employed as a chiral catalyst (20 mol%), **2** of 100% e.e. (room temp., 69% yield, optically active to *meso* = 85:15) was obtained again.

Compounds DBNE⁴ and DPMPM⁵ catalyse the enantioselective addition of diethylzinc to aromatic monoaldehydes such as benzaldehyde with 90–94% e.e. and with 97% e.e. respectively. According to eqn. (1), when the e.e. *x* is 90, 94 and 97%, the e.e. *y* should be 99.4, 99.8 and 99.95%, respectively.

The experimental results obtained in the present enantioselective diethylation of terephthalaldehyde are thus in good agreement with the results derived from eqn. (1).

The present considerations and results may be applied to other asymmetric reactions of monofunctional substances to obtain practically optically pure bifunctional substances possessing a *C*₂ symmetry axis.

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