Asymmetric Synthesis. Part 19. Asymmetric Autocatalysis of (R)-1-Phenylpropan-1-ol Mediated by a Catalytic Amount of Amine in the Addition of Diethylzinc to Benzaldehyde

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(R)-1-Phenylpropan-1-ol has been shown to undergo enantioselective autocatalysis in up to ca. 100% chemical yield and up to 49.2% ee, with retention of configuration, through the addition of diethylzinc to benzaldehyde mediated by a catalytic amount (4–6 mol%) of various amines.

Stereoselective addition of organometallic reagents to carbonyl compounds is important since it is one of the most efficient methods of generating optically active alcohols, important synthetic precursors of many natural products. Enantioselective addition of diethylzinc in this fashion is typical of such reactions.[1] Although much effort has been devoted to the search for structurally novel chiral catalysts[1b–d] which are of high efficiency, the role of the alcohol product in the asymmetric induction has been little studied. In the work of Wynberg et al.[2] and Kenso Soai et al.[3] the asymmetric autoinduction was obtained with an ee of up to 32% (<72% yield) and an ee of up to 35% (67% yield), respectively. Recently, Danda et al.[4] described a further example of enantioselective autoinduction in the asymmetric hydrocyanation of 3-phenoxybenzaldehyde catalysed by cyclo[(R)-phenylalanyl-(R)-histidyl].

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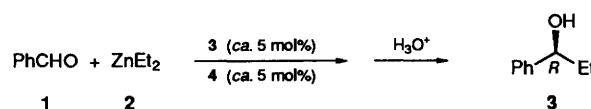
$$4 = Bu_3N, (c\text{-}C_6H_{11})_2NH, \text{piperidine}, PrNH_2, Pr^i_2NH$$

Scheme 1

Of the chiral catalysts used in the enantioselective addition of diethylzinc to benzaldehyde, we have found that chiral 2-tertiary aminoethanols are the most efficient.[1,5] Previously, we have shown that the hydroxy function of a catalyst plays an important role in achieving high stereoselectivity, the amino function playing a lesser role; however the latter may be more important in terms of the chemical reaction than of the asymmetric induction.[5] In view of this, the question arises as to whether an optically active alcohol as a chiral catalyst together with a little amine might not be equally efficient in such

Table 1 Asymmetric autocatalysis of (R)-1-phenylpropan-1-ol mediated by amines

			(R)-1-Phenylpropan-1-ol 3			
Entry[a]	Amount (W/mg) of catalyst[b] 3 [mol %]	Amount (W/mg) of amine[c] 4 [mol %]	Yield[d] (W/mg) [%]	$[\alpha]_D$ (t, c, CHCl₃)*	Ee(%)[e]	AI(%ee)[f]
1	6.3 [4.6]		60.0 [39.5]	+10.64 (30, 1.786)	23.3	14.3
2	7.0 [5.1]	Bu₃N 11.8 [6.3]	140.0 [97.8]	+20.75 (30, 0.988)	45.5	42.6
3	6.0 [4.4]	(c-C₆H₁₁)₂NH 11.5 [6.4]	143.0 [ca. 100]	+23.38 (30, 0.770)	51.3	49.2
4	6.6 [4.9]	Piperidine 6.5 [7.6]	120.0 [83.4]	+18.22 (30, 1.070)	40.0	36.5
5	8.1 [6.0]	PrNH₂ 3.7 [6.2]	78.0 [51.4]	+17.37 (22, 1.01)	38.1	30.9
6	7.8 [5.8]	Pr^i₂NH 7.0 [6.9]	100.0 [67.8]	+21.01 (22, 0.79)	46.1	41.5

* $[\alpha]_D$ values are recorded in units of 10^{-1} deg cm² g⁻¹. [a] The reaction (1:2:3:4 = 1:2: ca. 0.05: ca. 0.05, molar ratio, 1 mmol scale) was run at −78 °C initially then room temp. [b] $[\alpha]_D^{20}$ +44.15 (c, 0.95, CHCl₃), 96.8%ee. [c] Dried over 5Å MS and distilled before use. [d] Alcohol obtained, data in parentheses refer to the percentage yield of the autoinduction (i.e., the added amount of 3 was subtracted from the amount of 3 obtained). [e] Determined values, based on reported optical rotation, R form: $[\alpha]_D$ +45.6 (CHCl₃)[6]. [f] Values of the asymmetric autoinduction which can be calculated as follows: e.g. entry 1. Obtained W_3 = 60.0 mg, determined ee = 23.3% the percentage amount of R and S form enantiomer is

$$\begin{aligned} R + S &= 100\% & R &= 61.65\% \\ R - S &= 23.3\% & S &= 38.35\% \end{aligned}$$

so the amount (W) of R and S form enantiomer is

$$W_R = W_3 \cdot R = 60.0 \text{ mg} \times 61.65\% = 36.99 \text{ mg}$$

$W_S = W_3 \cdot S$ = 60.0 mg × 38.35% = 23.01 mg (newly generated), as 6.3 mg of the R form 3 was added, so the newly generated R form 3 is W_R' = W_R − 6.3 = 30.69 mg. Therefore, the asymmetric autoinduction (AI) is:

$$AI = \frac{W_R' - W_S}{W_R' + W_S} \times 100\% = 14.3\%ee$$

reactions. Moreover, if the alcohol were the same as the addition product, this would amount to asymmetric autoinduction.

Here we report our results for enantioselective autocatalysis employing a catalytic amount of (R)-1-phenylpropan-1-ol together with a catalytic amount of amine (primary, secondary or tertiary) in the enantioselective addition of diethylzinc to benzaldehyde.

From the reaction illustrated in Scheme 1 and the results summarized in Table 1 we can see that with (R)-1-phenylpropan-1-ol as the sole catalyst (entry 1), both asymmetric autoinductivity and the chemical yield were very low (14.3 ee and 39.5%, respectively). However, in the presence of a catalytic amount of amine (primary, secondary or tertiary) similar reactions (entries 2–6) gave increased asymmetric autoinductivity (from 16.6 to 34.9% ee) and increased chemical yields (from 11.9 to 60.5%). Of the entries 2–6, dicyclohexylamine effects the greatest promotion of asymmetric autoinduction and chemical reactivity (entry 3, AI 49.2% ee, CY ~ 100%) whilst propylamine (entry 5) shows the least. Tributylamine (entry 2) is more effective than propylamine (entry 5), diisopropylamine (entry 6) and piperidine (entry 4), but is less effective than dicyclohexylamine (entry 3).

The above results illustrate that in the addition of diethylzinc to benzaldehyde, amines can strongly promote the autocatalysis of (R)-1-phenylpropan-1-ol in terms both of its asymmetric induction and chemical reactivity; the more sterically hindered the amine the higher its ability to promote this activity.

Typical Experimental Procedure for the Asymmetric Auto-catalysis of (R)-1-*Phenylpropan-1-ol* (*Entry* 2).—In a flame-dried 20 cm^3 flask were placed (R)-1-phenylpropan-1-ol (7.0 mg, 5.1 mol equiv.), tributylamine (11.8 mg, 6.3 mol equiv.) and dry toluene (12 cm^3). Into this solution at −78 °C (solid CO$_2$–

acetone bath) was syringed diethylzinc (Aldrich, 1.0 mol dm^3 hexane solution; 2.2 cm^3) and the mixture was stirred for a few minutes. Freshly distilled benzaldehyde (106 mg, 1 mmol) was then added and the mixture stirred for *ca.* 48 h [monitoring by TLC: silica GF$_{254}$, eluent, CHCl$_3$–Et$_2$O, (8:1, v/v), R_f(3)0.56] at room temp., the solution was quenched by HCl (2 mol dm^3; 10 cm^3). The product (140.0 mg, 97.8%) was isolated by the customary work-up procedure. The ee value of the product was determined on a Perkin-Elmer 241 automatic polarimeter. The value of the asymmetric autoinduction can be calculated by the method indicated in note *f* to Table 1.

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