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Chiral Oxazaborolidines as Catalysts for the Enantioselective Addition of Diethylzinc to Aldehydes

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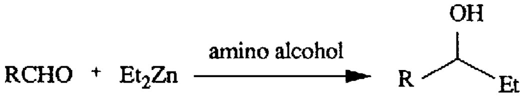
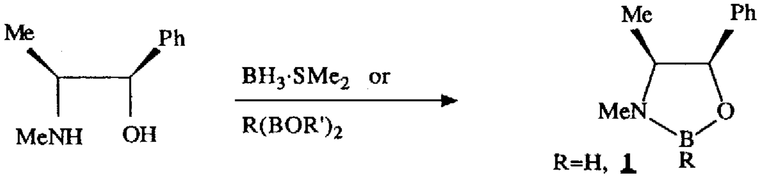
Summary. (4*S*, 5*R*)-3,4-dimethyl-5-phenyl-1,3,2-oxazaborolidine, 1, catalyzes the addition of diethylzinc to aldehydes to furnish secondary alcohols in up to 96% ee. This is the first example of a chiral boron intermediate for this reaction.

While the chemistry involving stoichiometric reactions of organoboranes has been amply investigated and shown to be rich and diversified[1], catalytic processes especially asymmetric, have been relatively neglected, and only recently have a number of enantioselective reactions catalyzed by chiral organoboranes appeared in the literature[2]. However, since many reactions are catalyzed by Lewis acids and since chiral organoboranes are readily accessible chiral Lewis acids, we have undertaken a program to develop new catalysts based on boron and to apply them to suitable reactions. The addition of diethylzinc, DEZ, to aldehydes is one such reaction. DEZ reacts with aldehydes very sluggishly at 25° C in non-coordinating solvents[3]. In 1984 Oguni and Omi reported that small amounts of amino alcohols greatly accelerated the reaction and induced optical activity, albeit modest, when optically active amino alcohols were involved[4] (eq 1).



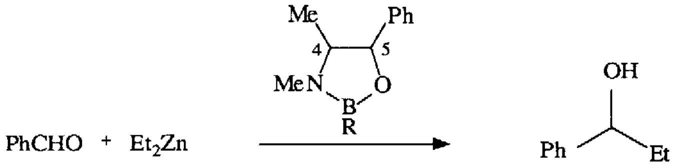
(1)

Subsequent workers increased the enantiomeric excess (ee) of the product alcohols but only at the expense of designing more and more complex amino alcohols[5]. Examination of the postulated mechanism of this reaction indicated to us that boron might well serve as the central metal in the template and by virtue of generally forming shorter B-O and B-N bonds than do other metals, possibly provide a superior catalytic system. In this communication we describe our initial efforts into asymmetric catalysis with chiral organoboranes in the particular case of the addition of DEZ to aldehydes. As structures for possible catalysts, we chose the oxazaborolidines [6]. As the amino alcohol moiety we selected ephedrine, both enantiomers of which are commercially available. The borolidines were prepared by heating the amino alcohol with either $BH_3 \cdot SMe_2$ or the appropriate boronate ester, $RB(OR')_2$ until two equivalents of either H_2 or R'OH had evolved (eq 2).



(2)

Table 1. Reaction of Diethylzinc with Benzaldehyde Catalyzed by Chiral Oxazaborolidines[a].



Entry	Config. of Catalyst	R	Time, h	% ee	Config. of Product
1	4S, 5R	Ph	60	47	R
2	4S, 5R	Me	24	78	R
3	4S, 5R	H	12	86	R
4	4R, 5S	H	12	85	S
5	4S, 5S	H	8	2	R
6	b	b	12	58	R
7	c	c	4	70	R
8	d	d	4	71	R

[a] Reactions were run at 0°C in toluene, 3 M in DEZ, in the presence of 5 mol % catalyst. [b] Catalyst prepared by mixing $AlMe_3$ and (-)-ephedrine. [c] Catalyst prepared from n-BuLi and (-)-ephedrine. [d] Catalyst prepared by mixing DEZ and (-)-ephedrine.

The results for the addition of DEZ to benzaldehyde for several catalysts are summarized in Table 1. For the sake of comparison, we also prepared catalysts based on Al, Li and Zn by reacting ephedrine with $AlMe_3$, *n*-BuLi and DEZ respectively. (Presumably, these catalysts contain Al, Li, or Zn atoms in place of boron. However, since the exact structure of these catalysts in solution are not known their representation at this point is merely speculative.) A comparison of the results obtained with these metallated oxaza-ring systems indicates that in the present case the results with Al (58% ee), Li (70% ee), and Zn (71% ee) are clearly inferior to that obtained with boron (86% ee). As regards the present series of oxazaborolidines the following generalizations apply: **1.** Both the rate and the ee are optimized when boron is unhindered (Table 1.). **2.** The *cis* configuration of C4/C5 is preferred to *trans*. Based on these results we selected **1**, or its enantiomer, for further study. **1** exists essentially as a monomer in solution (1 M in toluene) as determined by ^{11}B-NMR. To ascertain the stability of **1**, (and the other oxazaborolidines in the presence of DEZ), we added an equivalent of DEZ to **1**. No discernible change in the ^{11}B-NMR spectrum was observed for 24 h at 25° C, indicative that the borolidine ring had not been cleaved or that exchange between BH and DEZ had not occurred[7].

Aromatic aldehydes generally reacted with DEZ much faster than did aliphatic aldehydes. The optical inductions were good to excellent for aromatic aldehydes while the aliphatic aldehyde tested gave a product of only moderate ee[8]. Typical results are listed in Table 2.

Table 2. Reaction of DEZ and Various Aldehydes in the Presence of 1[a].

Entry	Aldehyde	Time, h	$[\alpha]_D$, c=5, $CHCl_3$	% ee	Abs. Config.
1	Benzaldehyde	30	+39.1	95[b]	R[d]
2	1-Methoxybenzaldehyde	48	+44.5	91[b]	R[e]
3	4-Methoxybenzaldehyde	48	+32.2	93[b]	R[f]
4	4-Chlorobenzaldehyde	48	+27.7	96[b]	R[f]
5	2-Furaldehyde	64	+16.1	66[c]	R[g]
6	Heptanal	88	-4.3	52[c]	R[f]

[a] All reactions were run at -25°C in toluene, 3 N in DEZ and 5 mol% catalyst. . Chemical yields in all cases were ≥ 85 %. [b] Determined as the (-)-menthyl chloroformate esters on a Supelcowax capillary column, 15 m. [c] Determined as the (+)-MTPA ester on a SPB-5 capillary column, 30 m. [d] Ref. 4. [e] Ref. 5a. [f] Ref 5f. [g] Tentatively assigned by analogy to the other compounds.

As regards the mechanism of this reaction induced by oxazaborolidines, we believe that an intermediate ternary complex is formed, consisting of the aldehyde complexed to boron and DEZ coordinated to either nitrogen or oxygen of the borolidine ring[9]. In addition since no precatalyst-catalyst equilibrium is operating in the present case as it is with the zinc derived catalyst[10], a linear relationship between the optical purity of the catalyst and the ee of the product should exist[11]. Indeed, we have found this to be the case, again indicative that a single monomeric oxazaborolidine species is involved in the catalysis.

In conclusion, this is the first example of the use of a chiral boron intermediate as a catalyst for the addition of an organometallic reagent to aldehydes. We are currently probing the precise mechanism of this reaction, an understanding of which should enable us to devise superior catalysts capable of handling both aromatic and aldehydes. Other asymmetric transformations amenable to catalysis by organoboranes are also being investigated and will be the subject of future publications.

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7. However, we have discovered that various boron esters do exchange with DEZ, the rate of exchange being proportional to the steric bulk of the alkoxy unit. Thus, B-methoxy-9-BBN completely exchanges with DEZ within 5 min at 25° C , each of the reactants being 1 M in toluene, while B-isopropoxy-9-BBN requires 3-4 h under the same conditions. B-t-butoxy-9-BBN does not exchange for at least 24 h. For a general treatise on the chemistry of dialkylzincs see: Boersma, J. In *Comprehensive Organometallic Chemistry;* Wilkinson, G. Ed.; Pergamon Press: Oxford, 1982; Vol. 2, p 823.

8. **Preparation of oxazaborolidine 1.** A solution of (1*R*, 2*S*)-(-)-ephedrine (8.25 g, 50 mmol) in anhydrous THF (50 mL) was treated with boron-methy lsulfide, BMS, (50 mmol, 5 mL of 10 M solution). The reaction mixture was stirred at 25° C for 1 h by which time one equiv of hydrogen had evolved. The volatiles were pumped off to furnish a white solid, ^{11}B-NMR ($\delta \sim$ 8 ppm). The solid was gradually heated to 100°C and maintained at that temperature until the seond equivalent of hydrogen had evolved. The product was distilled under reduced pressure to obtain pure 1 as a colorless liquid. Yield: 7.6 g (86 %); bp 110-112° C, 20 mm Hg; ^{11} B-NMR δ 25 ppm, d (J=160 Hz); IR$_{BH}$ 2562 cm^{-1}. **The preparation of (R)-(+)-1-phenyl-1-propanol is typical:** A solution of diethylzinc (12 mmol, 4 mL) in toluene was cooled to -25° C using a cryobath. The catalyst 1, (0.5 mmol, 1 mL of a 1 M solution) in toluene and benzaldehyde (10 mmol, 1.06 g) were then successively introduced into the reaction flask. A yellow color developed which gradually disappeared in the course of the reaction. A positive pressure of Ar was maintained inside the flask and the reaction was periodically monitored by GC (every 8 h), by which procedure the reaction was found to tail-off towards the end. (This could be prevented by using a larger excess of DEZ, ~ 50 %). At this stage the reaction mixture was diluted with ether (100 mL), transferred to a separatory funnel and cautiously washed with 2 N HCl followed by saturated brine. The organic phase was dried over anhydrous K_2CO_3 and concentrated under reduced pressure. The residue was purified by flash chromatography followed by short-path distillation to furnish (R)-(+)-1-phenyl-1-propanol. Yield: 1.2 g. (88 %); bp 105-107 °C, 20 mm Hg. The analysis for the enantiomeric excess was performed via the (-)-MCF ester on a 15 m Supelcowax capillary column: temp., 180°C, head pressure, 6 psi; R_t (for the major isomer) 10.8 min, 95% ee.

9. The steric environment around nitrogen and oxygen presumably determines the extent of coordination of DEZ with one or the other and in turn influences the magnitude of the optical induction. Unpublished observations.

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