Enantioselective addition of diethylzinc to aldehydes catalysed by a β-amino disulfide derived from L-proline

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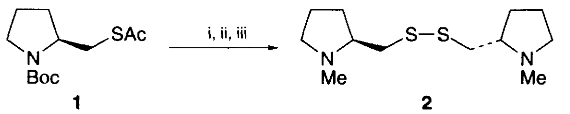
A novel β-amino disulfide 2 is prepared and is effective at catalytic levels (1.25–2.5 mol%) in the enantioselective addition of diethylzinc to aldehydes providing (*R*)-secondary alcohols in up to 99% ee.

The asymmetric nucleophilic addition of organometallic reagents to carbonyl groups constitutes an important preparation of chiral secondary and tertiary alcohols.[1] This importance has resulted in the development of a number of stoichiometric methods for the enantioselective addition of organometallic reagents to aldehydes and ketones. More significantly, the asymmetric nucleophilic addition of dialkylzinc reagents to carbonyl groups has been extensively studied since this process has been achieved catalytically using, principally, chiral β-amino alcohols which have proven to be highly effective catalysts.[1] Superior catalysts incorporating amino and sulfur or selenium groups have been reported recently. Thus, β-amino thiols and β-amino disulfides derived from ephedrine (0–90% ee),[2] norephedrine (62–100% ee)[3] or 2-amino-1,2-diphenylethan-1-ol (73–100% ee)[4] have been used as highly effective catalysts for the diethylzinc addition to aldehydes. Derivatives of γ-amino arenesulfanyls (69–99% ee)[5] and structurally analogous γ-amino arenediselenides (45–93% ee)[6] have also been shown to be effective catalysts for these enantioselective additions to aldehydes.

These impressive findings together with the availability of a wide variety of diorganozinc reagents carrying labile functionality[7] ensure the continued importance for the development of catalysts for this process. In particular, the development of improved catalysts derived from non-toxic and inexpensive starting materials would be of considerable utility in this important area of asymmetric synthesis. To this end, as part of our continuing interest in sulfur containing catalysts, reported herein is a new β-amino disulfide 2 derived from L-proline that is a highly effective catalyst for the enantioselective addition of diethylzinc to aldehydes. The chiral β-amino disulfide 2 was synthesised from the *N*-Boc thiol acetate 1, the synthesis of the latter we have reported previously.[8] Thus, lithium aluminium hydride reduction of 1 followed by treatment with aqueous acid and aerial oxidation afforded the disulfide 2[‡] (36%) (Scheme 1).

The disulfide 2 proved to be a very effective catalyst for the enantioselective addition of diethylzinc to aldehydes (Scheme 2). As summarised in Table 1, under generalised conditions [Et_2Zn (2 equiv.), 1.25–2.5% (mol/mol) of the catalyst 2, toluene, 0 °C],[§] all the aldehydes afforded the corresponding (*R*)-secondary alcohols in excellent yield ($\geq$76%) and in moderate to excellent ees (68.6–99%).



Scheme 1 *Reagents and conditions*: i, $LiAlH_4$, Et_2O, heat, 12 h; ii, 12 mol dm^{-3} HCl; iii, O_2, EtOH, 2 h

Several features of this study require further comment. Firstly, the extent of chiral induction is dependent on the nature of the aldehyde with the arylaldehydes giving excellent ees of $\geq$86.6%. In contrast, dihydrocinnamaldehyde and cinnamaldehyde (*i.e.* non α-branched aldehydes) give moderate ees of 68.6 and 70.2%, respectively. This decrease in ee on dialkylzinc catalysed addition to non α-branched aldehydes has been noted previously and the ee reported in this study for the diethylzinc addition to non α-branched aldehydes are in accord, or better, than those already reported.[3–6] Secondly, the ees show little variation on decreasing the amount of catalyst from 2.5 (86.6% ee) to 1.25 mol% (81.4% ee) for the addition of diethylzinc to benzaldehyde. This lack of response of the ee to the benzaldehyde/catalyst ratio indicates the complete formation of an active catalyst as suggested by Kellogg and coworkers.[2] Thirdly, the ees observed in this study using the β-amino disulfide 2 are remarkable in comparison with the analogous β-amino alcohols. Thus, Soai *et al.* have reported that racemic 1-phenylpropanol results when the related β-amino alcohol (*S*)-*N*-methylprolinol is used as a catalyst in the addition of diethylzinc to benzaldehyde. This dramatic increase in ee resulting from the use of the catalyst 2 again indicates the complete formation of an active catalyst. Finally, the (*R*)-configuration obtained in each of the secondary alcohols using the β-amino disulfide 2 as catalyst is in accord with the configurational rules reported by Noyori for β-amino alcohols.[1b] Modified versions of the above β-amino disulfide 2 are currently being investigated as improved catalysts in asymmetric carbon–carbon bond forming processes.

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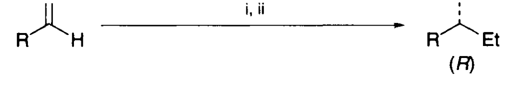

Scheme 2 *Reagents and conditions*: i, Et_2Zn (2 equiv), 2 (1.25–2.5 mol%), toluene, 0 °C, 48–72 h; ii, 1 mol dm^{-3} HCl

Table 1 Enantioselective addition of diethylzinc to aldehydes in the presence of 2[a]

R in RCHO	Yield (%)[b]	ee (%)[c] (configuration)
Ph[d]	76	86.6 (*R*)
Ph[e]	94	81.4 (*R*)
4-MeC_6H_4[d]	83	99.0 (*R*)
2-Naphthyl[d]	88	90.0 (*R*)
(*E*)-PhCH=CH[d]	96	70.2 (*R*)
$PhCH_2CH_2$[d]	77	68.6 (*R*)

[a] Reactions were carried out in toluene at 0 °C for 48–72 h using 2 equiv. of Et_2Zn. [b] Isolated yield for chromatographically pure material (> 97%). [c] Ees determined by HPLC using a Daicel chiralcel OD column. Absolute configuration determined from optical rotation. [d] Using 2.5 mol% of 2. [e] Using 1.25 mol% of 2.

(Edinburgh University) are warmly thanked, respectively, for providing the starting material for the synthesis of **1** and for the determination of the accurate mass of β-amino disulfide **2**.

Footnotes

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‡ *Selected spectroscopic data* for **2**: found MH$^+$ 261.1468 $C_{12}H_{25}N_2S_2$ requires 261.1459; δ_H ($CDCl_3$, 250 MHz) 3.11–3.07 (m, 1 H), 3.02 (dd, *J* 12.8, 3.4 Hz, 1 H), 2.73 (dd, *J* 12.8, 8.2 Hz, 1 H), 2.49–2.39 (m, 1 H), 2.36 (s, 3 H), 2.29–2.17 (m, 1 H), 2.11–1.97 (m, 1 H) and 1.85–1.59 (m, 3 H); δ_C ($CDCl_3$, 67.8 MHz) 65.88, 58.05, 44.59, 41.27 and 31.19; $[\alpha]_{20}^{D}$ −316 (*c* 0.47, $CHCl_3$).

§ In a typical experiment diethylzinc (1.87 cm^3 of a 1 mol dm^{-3} solution in hexane, 1.87 mmol) was added to a stirred solution of disulfide **2** (6.1 mg, 0.023 mmol) in anhydrous toluene (5 cm^3) under a nitrogen atmosphere. After stirring at room temperature for 2 h the solution was cooled to −27 °C, whereupon, freshly distilled aldehyde (0.937 mmol) was added and the resulting yellow solution was stirred at 0 °C for 48 h. At the completion of this period 1 mol dm^{-3} aqueous HCl was added (3 cm^3). The aqueous phase was extracted with dichloromethane (2 × 10 cm^3) and dried over sodium sulfate. Evaporation of the solvent and flash column chromatography (hexane–ethyl acetate) afforded the product alcohols in yields of 77–96%.

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