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# An L-proline-based β-amino tertiary thiol: synthesis and use as a catalyst in the enantioselective addition of diethylzinc to aldehydes

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**Abstract**

Two independent routes for the synthesis of the novel β-amino tertiary thiol **1** have been developed. Utilisation of this thiol in the enantioselective addition of diethylzinc to aldehydes provided (*R*)-secondary alcohols in ees of up to 64%. 

## 1. Introduction

The observation that amino sulfur catalysts offer improvements in enantioselectivity over their amino alcohol counterparts is known for a number of transition metal mediated carbon–carbon bond forming processes.[1–7] This has led to the development of a wide range of chiral sulfur/nitrogen chelate catalysts for the enantioselective 1,2-addition of dialkylzinc reagents to aldehydes.[1,2,5,8,9] Consequently, a number of years ago we initiated a programme for the development of syntheses of chiral β-amino disulfides from α-amino acids and investigated their use in a number of transition metal mediated processes.[5–8,10] In these previous studies, α-amino acids were identified as attractive starting points because such entities offer ready access to sterically demanding systems and also because of their low toxicity. In these earlier studies we concentrated on the synthesis and use of β-amino disulfides in line with the observations of Kellogg[1] that β-amino disulfides are far more stable than their β-amino thiol counterparts, the latter are readily oxidised to the former, even under carefully controlled conditions.

The active catalytic species in dialkylzinc promoted reactions using β-amino disulfides has been elegantly established by Kellogg.[1] Thus, the disulfide bond is cleaved by the dialkylzinc to give the catalytically productive zinc thiolate complex **A** (in a dimer/monomer manifold) together with a catalytically unproductive thioether **B** (Scheme 1).[11] In terms of stereochemical economy the use of disulfides is

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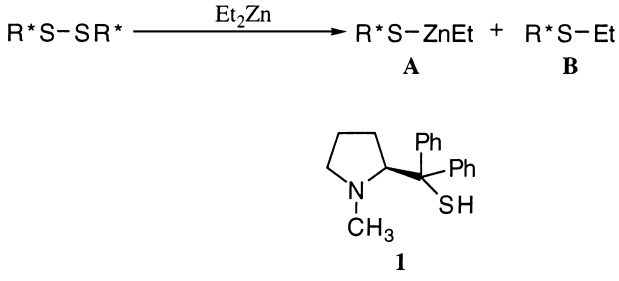
inefficient because 50% of the stereochemical information is lost as the stable thioether **B**. Consequently, this led us to the postulation that β-amino tertiary thiols, e.g. **1**, may be better catalyst systems since we anticipated that they would be more resistant to auto oxidation in comparison with their primary counterparts. This would lead to stable β-amino thiols and so improve the stereochemical economy over β-amino disulfides. Also, we hoped that the so-called 'magic diphenylmethanol effect'[12,13] would apply equally to the diphenylmethane thiol group in **1** and so lead to greatly enhanced enantioselectivities.




Scheme 1.

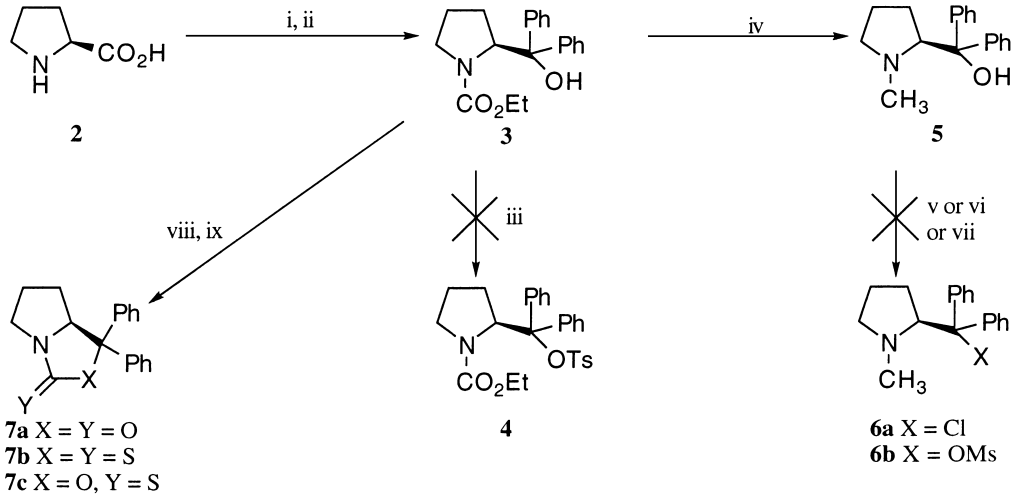
To our knowledge, β-amino tertiary thiols have not been prepared previously. However, Kellogg has reported the preparation of chiral pyridine tertiary thiols from thiofenchone.[14] In contrast, Chelucci et al. have recently tried, unsuccessfully, to prepare tertiary thiol pyridine ligands from the corresponding tertiary alcohols.[4] Seebach et al.,[15] have elegantly shown that the TADDOL systems can be converted into δ-amino tertiary thiols which were effective catalysts in enantioselective conjugate addition reactions.[16] Therefore, we set out to establish if β-amino tertiary thiol **1** could be prepared as well as assessing its use as a chiral catalyst in the enantioselective addition of dialkylzinc reagents to aldehydes.

## 2. Results and discussion

### 2.1. Synthesis of thiol *1*

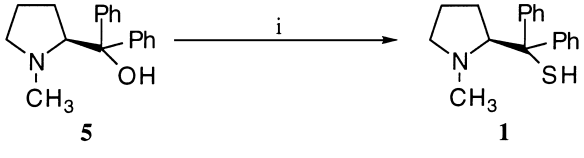
Initially, we anticipated that the β-amino tertiary thiol **1** could be accessed from L-proline **2** using our previously developed methodology for the synthesis of β-amino primary disulfides from amino acids.[5,8,10] Thus, treatment of L-proline **2** with ethyl chloroformate and potassium carbonate in methanol (89% after distillation) followed by reaction with excess phenylmagnesium bromide afforded the tertiary alcohol **3** in 90% yield after purification (Scheme 2).[17] Attempts to convert the tertiary alcohol **3** into the tosylate **4**, using a variety of bases (pyridine, DMAP, NaH or MeLi) in conjunction with tosyl chloride, resulted in recovery of starting material. Consequently, the *N*-carbamate moiety in **3** was reduced with lithium aluminium hydride in THF at reflux to afford the corresponding *N*-methyl derivative **5** in 88% recrystallised yield. Attempted conversion of the *N*-methyl tertiary alcohol **5** into the corresponding mesylate **6a** (X=OMe) gave starting material upon treatment with mesyl chloride or mesic anhydride and various bases ($Et_3N$, DMAP, MeLi or BuLi). In contrast, reaction of the *N*-methyl tertiary alcohol **5** with thionyl chloride under conditions developed by Deyrup et al. for the chlorination of aziridine tertiary alcohols[18] led to complete decomposition. Alternatively, treatment of *N*-methyl tertiary alcohol **5** with HCl gas in dichloromethane failed to yield the chloride **6b** (X=Cl) but afforded recovered starting material. Studies aimed at accessing the tertiary thiol **1** by conversion of the known diphenyl[1,3]oxazol-3-one **7a** (X=Y=O)[17b,c] into the [1,3]thiazol-3-thione **7b** (X=Y=S) using a variety of thionation reagents

either led to low yields of the required **7b** ($P_4S_{10}$ or Davy's reagent ethyl) or to the generation of the [1,3]oxazol-3-thione **7c** (X=O, Y=S) (Lawesson's reagent).



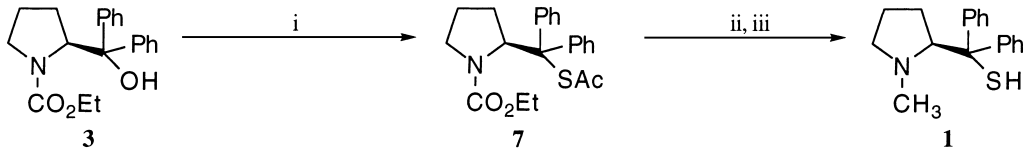

Scheme 2. Reagents and conditions: (i) EtOCOCl, MeOH, $K_2CO_3$; (ii) PhMgBr, THF; (iii) TsCl, base (pyr. or DMAP or NaH or MeLi); (iv) $LiAlH_4$, THF, △; (v) MsCl or $Ms_2O$, base ($Et_3N$ or DMAP or MeLi or BuLi); (vi) $SOCl_2$; (vii) HCl–$CH_2Cl_2$; (viii) KOH, MeOH; (ix) Lawesson's or $P_4S_{10}$ or Davy's reagent ethyl ($(EtSPS_2)_2$), toluene, △

The failure to introduce a suitable leaving group or efficiently insert a sulfur at the tertiary position of alcohols **3** or **5** led to a reassessment of the synthetic protocol. In this context, Nishio has shown that tertiary alcohols can be converted directly into tertiary thiols using Lawesson's reagent.[19] However, dehydration products can predominate when the tertiary alcohol contains a β hydrogen. Indeed, exclusive dehydration was observed by Chelucci et al. upon treatment of diphenylhydroxymethyl or dimethylhydroxymethyl tetrahydroquinolines with Lawesson's reagent.[4] However, treatment of *N*-methyl tertiary alcohol **5** with Lawesson's reagent under precisely controlled conditions (toluene, Δ, 7 min) gave, reproducibly, the requisite tertiary thiol **1** in 42% yield (24.6% overall yield, four steps from L-proline **2**) (Scheme 3). The tertiary thiol **1** appeared to be stable to auto oxidation and showed no evidence of disulfide formation, however, it was unstable to visible light showing rapid decomposition.




Scheme 3. Reagent and conditions: (i) 0.53 equiv. Lawesson's reagent, toluene, △

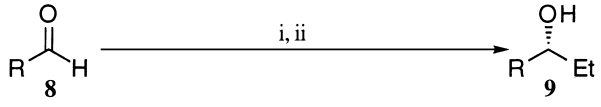
Although the tertiary thiol **1** had been successfully prepared, the final Lawesson's reaction (Scheme 3) led to moderate yields for the conversion of **5** into **1**. Consequently, alternative routes to tertiary thiol **1** were assessed. In this context, Gauthier et al. have shown that $S_N1$ active alcohols can be converted into the corresponding thiol esters upon treatment with zinc iodide and a thiol acid.[20] Thus, reaction of carbamate tertiary alcohol **3** with zinc iodide and thioacetic acid afforded the carbamate thioacetate **7** in 55% yield. Lithium aluminium hydride reduction[5] of carbamate thioacetate **7** followed by acid treatment gave the tertiary thiol **1** in 36% yield (15.9% overall yield, four steps from L-proline **2**) (Scheme 4) which was identical to that prepared above.




Scheme 4. Reagents and conditions: (i) 1 equiv. $ZnI_2$, 2.15 equiv. AcSH, $ClCH_2CH_2Cl$; (ii) $LiAlH_4$, THF, △; (iii) 1.2 M HCl

### 2.2. Enantioselective catalytic addition of diethylzinc to aldehydes

Successful access to the β-amino tertiary thiol **1** allowed an investigation of its ability to act as a catalyst in the enantioselective 1,2-addition of diethylzinc to aldehydes. As a result of the photolability of thiol **1** all reactions were carried out using freshly prepared material and were conducted at 0°C in toluene for a variety of aldehydes (Scheme 5, Table 1).




Scheme 5. Reagents and conditions: (i) $Et_2Zn$ (2 equiv.), **1** (5 mol%), toluene, 0°C, 48–72 h; (ii) 1 M HCl

Initial studies on the catalytic efficiency of thiol **1** in the diethylzinc addition to benzaldehyde, indicated no variation in the enantioselectivity on increasing the concentration of the thiol **1** from 2.5 to 5 mol% (entries 1 and 2) but perhaps improved the efficiency. The lack of sensitivity of the enantioselectivity to the thiol concentration suggests the complete formation of an active catalyst, in contrast to an equilibrium arrangement.[1,5] Consequently, the remaining studies were carried out using 5 mol% of **1**.

In general terms the enantioselectivities achieved using the tertiary thiol **1** in the enantioselective addition of diethylzinc to aldehydes (6–64% ee, Scheme 5, Table 1) are disappointing. Indeed, the tertiary

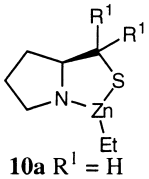
Table 1
Enantioselective addition of diethylzinc to aldehydes in the presence of **1**

| Entry | R in RCHO | Yield (%)[a] | e.e. (%)[b] (configuration)[c] |
|---|---|---|---|
| 1 | Ph[d] | 74 | 44 (*R*) |
| 2 | Ph | 81 | 44 (*R*) |
| 3 | 4-$MeC_6H_4$ | 80 | 56 (*R*) |
| 4 | 4-$MeOC_6H_4$ | 92 | 30 (*R*) |
| 5 | 2-$MeOC_6H_4$ | 87 | 64 (*R*) |
| 6 | 2-Naphthyl | 49 | 56 (*R*) |
| 7 | (E)-PhCH=CH | 90 | 16 (*R*) |
| 8 | $PhCH_2CH_2$ | 68 | 8 (*R*) |

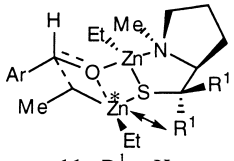
[a]Isolated yield for chromatographically pure material (> 97 %). [b]Enantiomeric excesses determined by HPLC using Daicel chiralcel OD or OB columns. [c]Absolute configuration determined from the known elution order of the isomers.[5,21] [d]Using 2.5 mol% of **2**.

thiol **1** shows a marked decrease in enantioselectivity in comparison to our related β-amino disulfide derived from L-proline (68–99% ee).[5] These observations indicate that the 'magic diphenylmethanol effect' cannot be directly applied to the corresponding sulfur analogues. A possible explanation for these differences is to consider the alternative transition states for the formation of the (*R*)- and (*S*)-alcohols.

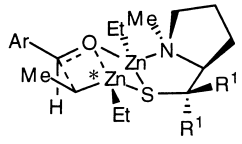
The currently accepted mechanism for the β-amino alcohol catalysed addition of dialkylzinc to aldehydes has been reviewed[22] and applied directly to amino thiols[2c] and zinc arene thiolate catalysts.[9e] Transition state modelling has been carried out on amino alcohols at the ab initio level[23] and semi emperically.[24,25] The core structural features from the ab initio calculations have been used as the basis for PM3 calculations of the transition states for an azabornylmethanethiol catalyst.[3]




**10a** $R^1$ = H
**10b** $R^1$ = Ph




**11a** $R^1$ = H
**11b** $R^1$ = Ph
*anti anti Re* (major TS‡)




**12a** $R^1$ = H
**12b** $R^1$ = Ph
*syn anti Si* (minor TS‡)

Based on the foregoing body of evidence it can be presumed that the active catalytic species for our proline derived disulfide[5] and thiol **1** are the tricoordinate thiazazincolidines **10a** ($R^1$=H) and **10b** ($R^1$=Ph), respectively. The tricoordinate thiazazincolidines **10a**,**b** act as bifunctional catalysts that assemble the aldehyde and dialkylzinc, leading to the product forming transition states. By analogy with the PM3 calculations on azabornylmethanethiol catalysts by Hongo and co-workers[3] and the rationalisation of azanorbornylmethanol enantioselectivities by Andersson and co-workers,[26] we propose that structures **11a**,**b** and **12a**,**b** are the two product forming transition states. The major *anti anti Re* transition states **11a**,**b** lead to alkyl addition to the *Re* face of the aldehyde to afford the (*R*)-alcohol while the minor *syn anti Si* transition states lead to the formation of the (*S*)-alcohol.[27] In the case of the active catalyst **10b** ($R^1$=Ph), the major transition state **11b** ($R^1$=Ph) is destabilised by steric interaction between the *pro-S* $R^1$ group and Zn*. In the minor transition state **12b**, such destabilisation does not occur and so the energies of the two transition states converge with concomitant reduction of enantioselectivity. In the case of the catalytic species **10a** ($R^1$=H), steric repulsion between the *pro-S* hydrogen and Zn* in the major transition state **11a** is less significant, so the differences in free energies between **11a** and **12a** is maintained. Consequently, catalyst **10a** produces much higher enantioselectivities in the diethylzinc addition to aldehydes.[5]

As sterically demanding aldehydes would lead to a destabilisation of transition state **12b** ($R^1$=Ph) relative to transition state **11a** ($R^1$=Ph) then it would be expected that such aldehydes would lead to higher enantioselectivities. This is the experimental observation, thus, *ortho* anisaldehyde (entry 5, 64% ee) and naphthaldehyde (entry 6, 56% ee) furnish the highest enantiomeric excesses. In contrast, the non-α-branched aldehydes cinnamaldehyde (entry, 7, 16% ee) and dihydrocinnamaldehyde (entry 8, 8% ee) provide the poorest enantioselectivities.

## 3. Conclusions

Although the synthesis of proline-based β-amino tertiary thiol **1** proved, initially, to be problematic, two independent syntheses were successfully carried out. The first route involved the Lawesson's reagent mediated conversion of a β-amino tertiary alcohol into β-amino tertiary thiol **1**. The second route required

the zinc iodide-promoted $S_N1$ conversion of a tertiary alcohol into a tertiary thioester, followed by subsequent reduction. The β-amino tertiary thiol **1** appeared to be stable to auto-oxidation with no evidence for disulfide formation, however, it was degraded by visible light. Utilisation of β-amino tertiary thiol **1** as a catalyst in the enantioselective addition of diethylzinc to aldehydes led to disappointing enantiomeric excesses (8–64% ee). These results were rationalised in terms of a consideration of the two likely transition states in conjunction with our previously reported results for a β-amino primary disulfide.[5]

The observations and rationalisations reported in this study are being utilised to design novel improved catalysts for transition metal mediated asymmetric reactions with a view to providing an experimental basis for our conclusions.[21]

## 4. Experimental

### 4.1. Instrumentation

Melting points were determined on a Reichert 7905 hot stage and are uncorrected. Optical rotations were measured at 20°C in a 1 mL cell with a pathlength of 10 cm using a Perkin–Elmer 341 polarimeter. The $[\alpha]_D$ values are given in $10^{-1}$ deg cm$^2$ g$^{-1}$ and the concentrations are given in g/100 cm$^3$. $^1$H NMR spectra were recorded on Brucker WM-250, Jeol 270, or Brucker 400 spectrometers in the indicated solvents operating at 250, 270 or 400 MHz, respectively. $^{13}$C NMR spectra were obtained on the same instruments operating at 62.89, 67.80, and 100 MHz, respectively. Infra red (IR) spectra were recorded on a Nicolet Impact 400D FTIR spectrometer either as liquid films or as 1–2% solutions in $CCl_4$. Mass spectra were recorded on a Jeol JMS AX505 spectrometer. Chiral HPLC analysis was performed using an Applied Chromatography Systems (ACS) Model 351 isocratic pump with the indicated flow rates and solvents. The columns used were either Daicel Chiralcel OB or OD columns (250×4.6 mm). The peaks were detected with an ACS Model 750/12 UV detector set at 254 nm and an ACS Chiramonitor. The data was collected on a Viglen computer fitted with a SUMMIT data card and the chromatograms were integrated using COMUS SUMMIT software.

### 4.2. General methods

All reactions were carried out under an atmosphere of nitrogen in oven dried glassware (140°C). Anhydrous solvents were obtained using standard procedures: methanol ($Mg(OMe)_2$), THF (K metal), toluene (Na metal) and dichloroethane (NaH). Flash column chromatography was performed according to the procedure of Still et al.[28] using silica gel (230–400 mesh) or neutral alumina where specified.

### 4.3. (S)-Proline-N-ethyl carbamate methyl ester[17]

This compound was prepared according to literature procedures except that it was purified by distillation before use to afford a colourless oil (89%), bp 78–82°C @ 0.13 mmHg (found: C, 53.60; H, 7.56; N, 6.81; calculated for $C_9H_{15}NO_5$: C, 53.72; H, 7.51; N, 6.96); $[\alpha]=-75.1$ (*c* 1.03, $CHCl_3$); $\nu_{max}$ (liq. film)/cm$^{-1}$ 1747 (ester C=O), 1700 (carbamate C=O); $\delta_H$ (400 MHz, $CD_3NO_2$, 80°C) 1.24 (t, *J*=7, 3H, C*H*$_3$CH$_2$O), 1.87–2.02 (m, 3H, C-4 CH$_2$+H-3), 2.25–2.32 (m, 1H, H-3), 3.44–3.51 (m, 2H, C-5 CH$_2$), 3.72 (s, 3H, CH$_3$O), 4.07–4.15 (m, 2H, CH$_3$C*H*$_2$O), 4.29–4.34 (m, 1H, H-2); $\delta_C$ (100 MHz,

$CD_3NO_2$, 80°C) 15.28 ($CH_3$), 25.14 ($CH_2$), 31.63 ($CH_2$), 48.01 (C-5), 52.79 (C-2), 60.76 ($OCH_3$), 62.43 ($CH_2O$), 156.49 (NC=O), 175.13 ($CO_2$) (found: $MH^+$ 202.1096; calculated for $C_9H_{15}NO_5$: 202.1080).

### 4.4. Ethyl (S)-(−)-2-[hydroxy(diphenyl)methyl]-1-pyrrolidinecarboxylate[17]

This compound was prepared according to literature procedures except that it was purified before use by flash column chromatography eluting with 28% ethyl acetate–hexane which afforded white needles (90%), mp 115–116.5°C (hexane) (found: C, 73.65; H, 7.33; N, 4.6; calculated for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.3); [α]=−146 (*c* 1.04, $CHCl_3$); $\nu_{max}$ ($CCl_4$)/$cm^{-1}$ 3540–3200 (OH), 1674, 700; $\delta_H$ (270 MHz, $CDCl_3$) 0.68–0.9 (m, 1H, H-5), 1.19 (t, *J*=7, 3H, $CH_3$), 1.41–1.53 (m, 1H, H-4), 1.88–1.97 (m, 1H, H-3), 1.99–2.17 (m, 1H, H-3), 2.91–1.99 (m, 1H, H-5), 3.42 (dd, *J*=18.4, 7.8, 1H, H-4), 4.04–4.17 (m, 2H, $CH_2O$), 4.93 (dd, *J*=8.9, 3.5, 1H, H-2), 7.21–7.42 (m, 10H, ArH); $\delta_C$ (100 MHz, $CDCl_3$) 15.05 ($CH_3$), 23.34 ($CH_2$), 30.04 ($CH_2$), 48.13 (C-5), 62.32 ($OCH_2$), 66.30 (C-2), 81.99 (COH), 127.28, 127.57, 127.75, 127.99, 128.29, 128.85, 129.05, 129.54 (all ArC-H), 144.07, 146.76 (both ArC), 158.77 (C=O) (found: $MH^+$ 326.1758; calculated for $C_{20}H_{23}NO_3$: 326.1756).

### 4.5. (S)-(+)-Diphenyl(1-methylpyrrolidin-2-yl)methanol

To a stirred solution of ethyl (*S*)-(−)-2-[hydroxy(diphenyl)methyl]-1-pyrrolidinecarboxylate (1.55 g, 4.77 mmol) in anhydrous THF at 0°C under a nitrogen atmosphere was added, portionwise, lithium aluminium hydride (0.364 g, 9.59 mmol). The resulting suspension was heated under reflux for 2 h, whereupon it was cooled to 0°C and water (20 mL) was added. The mixture was acidified to pH 3 with 1 M HCl and washed with ether (20 mL). The resulting aqueous layer was made alkaline with 11 M NaOH, filtered and the filtrate was washed with ethyl acetate (20 mL). The layers were separated and the aqueous phase was washed with dichloromethane (×2, 20 mL). The combined organic extracts were dried ($Na_2SO_3$), filtered and evaporated to afford colourless plates (1.12 g, 4.19 mmol, 88%), mp 70–71°C (hexane) (literature mp 68.5–68.9°C[13]) (found: C, 81.06; H, 7.93; N, 5.16; calculated for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.21); [α]=+56.7 (*c* 1.04, $CHCl_3$) (literature [α]=+57 (*c* 1, $CHCl_3$)[13]); $\nu_{max}$ ($CCl_4$)/$cm^{-1}$ 3550–3200 (OH), 2790, 704; $\delta_H$ (270 MHz, $CDCl_3$) 1.56–1.75 (m, 3H, H-3 and C-4 $CH_2$), 1.81 (s, 3H, $NCH_3$), 1.84–1.99 (m, 1H, H-3), 2.37–2.48 (m, 1H, H-5), 3.08–3.13 (m, 1H, H-5), 3.62 (dd, *J*=9.2, 4, 1H, H-2), 4.79 (bs, 1H, OH), 7.09–7.16 (m, 2H, Ar-H), 7.23–7.29 (m, 4H, Ar-H), 7.51–7.65 (m, 4H, Ar-H); $\delta_C$ (67.8 MHz, $CDCl_3$) 24.24 ($CH_2$), 30.09 ($CH_2$), 43.18 ($CH_3N$), 72.21 (C-2), 77.75 (COH), 125.65, 125.69, 126.34, 128.22, 146.91, 148.43 (all ArC) (found: $MH^+$ 268.1698; calculated for $C_{18}H_{21}NO$: 268.1701)

### 4.6. (S)-(+)-Diphenyl(1-methylpyrrolidin-2-yl)methanethiol

A stirred suspension of (*S*)-(+)-diphenyl(1-methylpyrrolidin-2-yl)methanol (99.5 mg, 0.373 mmol) and Lawesson's reagent (80.9 mg, 0.2 mmol) in anhydrous toluene (12 mL) was heated to reflux for 7 min. The resulting solution was cooled to 0°C and the solvent removed in vacuo. The resulting residue was filtered through a short plug of neutral alumina eluting with dichloromethane, evaporation of the solvent afforded a blue oil. Column chromatography of this residue on neutral alumina eluting with dichloromethane afforded a light yellow oil (44.7 mg, 0.158 mmol, 42%); [α]=+260 (*c* 0.955, $CHCl_3$); $\nu_{max}$ (liq. film)/$cm^{-1}$ 2956, 2847, 2785, 2785, 2570–2360 (SH), 748, 699; $\delta_H$ (270 MHz, $CDCl_3$) 1.62 (s, 3H, $NCH_3$), 1.64–1.86 (m, 2H, H-3/4), 2.04–2.13 (m, 1H, H-4), 2.16–2.25 (m, 1H, H-3), 2.34–2.41 (m, 1H, H-5), 3.07 (t, *J*=7.6, 1H, H-5), 3.53 (dd, *J*=9.2, 3.2, 1H, H-2), 7.11–7.27 (m, 8H, Ar-H),

7.39 (d, *J*=7, 2H, Ar-H), 7.56 (d, *J*=7, 2H, Ar-H); $\delta_C$ (67.8 MHz, $CDCl_3$) 25.39 ($CH_2$), 32.76 ($CH_2$), 44.59 ($NCH_3$), 59.89 (C-5), 66.09 (C-S), 74.3 (C-2), 126.72, 127.01, 128.12, 128.49, 129.17, 129.41 (all ArC-H), 146.79, 147.61 (both ArC); m/z (CI) 284 ($MH^+$, 75%), 250 ($MH^+$–$H_2S$, 100%) (found: $MH^+$ 284.1467; $C_{18}H_{22}NS$ requires: 284.1473)

### *4.7. Ethyl (S)-(−)-2-[(acetylsulfanyl)(diphenyl)methyl]-1-pyrrolidinecarboxylate*

To a stirred suspension of zinc iodide (225.3 mg, 0.706 mmol) in anhydrous dichloroethane (7 mL) was added a solution of ethyl (*S*)-(−)-2-[hydroxy(diphenyl)methyl]-1-pyrrolidinecarboxylate (207.1 mg, 0.637 mmol) in dichloroethane (4 mL) under a nitrogen atmosphere. To the resulting suspension was added thiolacetic acid (125 μL, 1.54 mmol) and the solution was stirred for 5 h. At the completion of this period, water (25 mL) was added and the layers were separated. The aqueous phase was extracted with dichloromethane (×2, 15 mL) and the combined organic layers were dried ($Na_2SO_4$), filtered and evaporated to afford a yellow oil. Purification by flash column chromatography eluting with hexane:ethyl acetate (68:32) afforded white needles (134.8 mg, 0.35 mmol, 55%), mp 140.5–141.5°C (hexane) (found: C, 68.61; H, 6.41; N, 3.52; $C_{22}H_{25}NO_3S$ requires: C, 68.9; H, 6.57; N, 3.65); $[\alpha]$=−231.4 (*c* 0.98, $CHCl_3$); $\nu_{max}$ ($CCl_4$)/$cm^{-1}$ 2982, 1712 (C=O), 704, 630; $\delta_H$ (400 MHz, $CD_3NO_2$, 80°C) 0.37–0.51 (m, 1H, H-5), 1.26 (t, *J*=7, 3H, C*H*$_3$CH$_2$), 1.42–1.52 (m, 1H, H-4), 2.0–2.07 (m, 1H, H-3), 2.12 (s, 3H, $CH_3$C=O), 2.29–2.32 (m. 1H, H-3), 2.66–2.72 (m, 1H, H-5), 3.43–3.47 (m, 1H, H-4), 4.02–4.18 (m, 1H, $CH_3$C*H*HO), 4.32–4.34 (m, 1H, $CH_3$CH*H*O), 5.67 (dd, *J*=8.8, 1.9, 1H, H-2), 7.24–7.4 (m, 6H, ArH), 7.41–7.42 (m, 2H, ArH), 7.59–7.6 (m, 2H, ArH); $\delta_C$ (100 MHz, $CD_3NO_2$, 80°C) 15.34 (*C*$H_3$C$H_2$O), 23.98 ($CH_2$), 30.71 ($CH_2$), 31.71 ($CH_3$C=O), 50.16 (C-5), 62.56 ($CH_2$O), 63.73 (C-2), 69.84 (C-S), 128.12, 128.4, 129.18, 131.56, 131.98 (all ArC-H), 142.82, 145.35 (both ArC), 158.96 ($CO_2$), 194.47 (SC=O) (found: $MH^+$ 384.1642; $C_{22}H_{26}NO_3S$ requires: 384.1633).

### *4.8. (S)-(+)-Diphenyl(1-methylpyrrolidin-2-yl)methane thiol via reduction of ethyl 2-[(acetylsulfanyl)(diphenyl)methyl]-1-pyrrolidinecarboxylate*

To a stirred suspension of lithium aluminium hydride (46.2 mg, 1.217 mmol) in anhydrous THF (3 mL) at 0°C under a nitrogen atmosphere was added, dropwise, a solution of ethyl 2-[(acetylsulfanyl)(diphenyl)methyl]-1-pyrrolidinecarboxylate (134.8 mg, 0.35 mmol) in dry THF (4 mL). The resulting suspension was heated to reflux for 7 h, whereupon it was cooled to 0°C and water (90 μL, 5 mmol) was added followed by 1.2 N HCl (1.2 mL). The organic layer was decanted from the solids and filtered through anhydrous sodium sulfate. The remaining solids were washed with dichloromethane (×3, 15 mL). The combined organic layers were evaporated and column chromatography on neutral alumina eluting with dichloromethane afforded a light yellow oil (36.1 mg, 0.127 mmol, 36%). The spectroscopic properties of this material were identical to those described above.

### *4.9. Addition of diethylzinc to aldehydes*

To a solution of the freshly prepared thiol (14.3 mg, 0.05 mmol) in anhydrous toluene (5 mL) under a nitrogen atmosphere was added diethylzinc (2 mL, 1 M solution in hexane, 2 mmol). After stirring at room temperature for 2 h the solution was cooled to −27°C, whereupon freshly distilled aldehyde was added (1 mmol) and the resulting yellow solution was stirred at 0°C for 48 h. At the completion of this period 1 M aqueous hydrochloric acid was added. The aqueous phase was extracted with dichloromethane

(2×10 mL) and dried over sodium sulphate. Filtration and evaporation of the solvent followed by flash column chromatography (hexane:ethyl acetate) afforded the product alcohols.

*4.9.1. 1-Phenyl-1-propanol*

Colourless oil (108 mg, 0.79 mmol, 81%) after purification by flash column chromatography (hexane:ethyl acetate, 82:18): $\nu_{max}$ (liq. film)/cm$^{-1}$ 3680–3100 (OH), 3030, 762, 700; $\delta_H$ (270 MHz, $CDCl_3$) 0.87 (t, *J*=7.4, 3H, C*H*$_3$CH$_2$), 1.62–1.83 (m, 2H, CH$_3$C*H*$_2$), 2.38 (s, 1H, OH), 4.51 (t, *J*=6.6, H-1), 7.21–7.35 (m, 5H, ArH); $\delta_C$ (68.7 MHz, $CDCl_3$) 10.13 (C-3), 31.82 (C-2), 75.91 (C-1), 127.32 (C-2′,6′), 127.41 (C-4′), 128.06 (C-3′,5′), 144.61 (C-1′) (found: M$^{+\cdot}$ 136.0886; calculated for $C_9H_{12}O$: 136.0888). The ee was determined by HPLC analysis using a Daicel Chiralcel OD column with 1% 2-propanol–hexane (flow rate 1 mL min$^{-1}$): (*R*)-1-phenyl-1-propanol 28 min, (*S*)-1-phenyl-1-propanol 35.1 min.

*4.9.2. 1-(4-Methylphenyl)-1-propanol*

Colourless oil (120.6 mg, 0.804 mmol, 80%) after purification by flash column chromatography (hexane:ethyl acetate, 4:1): $\nu_{max}$ (liq. film)/cm$^{-1}$ 3710–3090 (OH), 3020, 816; $\delta_H$ (270 MHz, $CDCl_3$) 0.86 (t, *J*=7.4, 3H, C*H*$_3$CH$_2$), 1.59–1.84 (m, 2H, CH$_3$C*H*$_2$), 2.31 (s, 3H, ArCH$_3$), 2.45 (s, 1H, OH), 4.46 (t, *J*=6.6, 1H, H-1), 7.11 (ABd, *J*=8.2, 2H, H-3′,5′), 7.17 (ABd, *J*=8.2, 2H, H-2′,6′); $\delta_C$ (68.7 MHz, $CDCl_3$) 10.30 (C-3), 21.20 (ArCH$_3$), 31.87 (C-2), 75.85 (C-1), 126.09 (C-2′,6′), 128.66 (C-3′,5′), 137.07 (C-4′), 141.81 (C-1′) (found: M$^{+\cdot}$ 150.1054; calculated for $C_{10}H_{14}O$: 150.1045). The ee was determined by HPLC analysis using a Daicel Chiralcel OB column with 1% 2-propanol–hexane (flow rate 0.7 mL min$^{-1}$): (*R*)-1-(4-methylphenyl)-1-propanol 28.3 min, (*S*)-1-(4-methylphenyl)-1-propanol 37.9 min.

*4.9.3. 1-(4-Methoxyphenyl)-1-propanol*

Colourless oil (153.8 mg, 0.927 mmol, 93%) after purification by flash column chromatography (hexane:ethyl acetate, 72:28): $\nu_{max}$ (liq. film)/cm$^{-1}$ 3700–3100 (OH), 2836, 831; $\delta_H$ (270 MHz, $CDCl_3$) 0.93 (t, *J*=7.3, 3H, C*H*$_3$CH$_2$), 1.34–1.93 (m, 2H, CH$_3$C*H*$_2$), 2.66 (s, 1H, OH), 3.84 (s, 3H, OCH$_3$), 4.54 (t, *J*=6.8, 1H, H-1), 6.93 (d, *J*=8.6, 2H, H-3′,5′), 7.27 (d, *J*=8.6, 2H, H-2′,4′); $\delta_C$ (67.8 MHz, $CDCl_3$) 10.29 (C-3), 31.82 (C-2), 55.28 (OCH$_3$), 75.56 (C-1), 114.15 (C-3′,5′), 127.73 (C-2′,4′), 136.93 (C-1′), 158.92 (C-4′) (found: M$^{+\cdot}$ 166.0985; calculated for $C_{10}H_{14}O_2$: 166.0994). The ee was determined by HPLC analysis using a Daicel Chiralcel OD column with 2.5% 2-propanol–hexane (flow rate 0.7 mL min$^{-1}$): (*R*)-1-(4-methoxyphenyl)-1-propanol 33.4 min, (*S*)-1-(4-methoxyphenyl)-1-propanol 37.4 min.

*4.9.4. 1-(2-Methoxyphenyl)-1-propanol*

Colourless oil (143.5 mg, 0.864 mmol, 87%) after purification by flash column chromatography (hexane:ethyl acetate, 97:3): $\nu_{max}$ (liq. film)/cm$^{-1}$ 3660–3135 (OH), 2836, 754; $\delta_H$ (270 MHz, $CDCl_3$) 0.92 (t, *J*=7.3, 3H, C*H*$_3$CH$_2$), 1.71–1.82 (m, 2H, CH$_3$C*H*$_2$), 2.85 (s, 1H, OH), 4.77 (t, *J*=6.5, 1 H, H-1), 6.22 (dd, *J*=7.6, 1, 1H, H-3′), 6.91 (td, *J*=7.6, 1, 1H, H-5′), 7.21 (td, *J*=7.6, 1.6, 1H, H-4′), 7.27 (dd, *J*=7.6, 1.6, 1H, H-6′); $\delta_C$ (67.8 MHz, $CDCl_3$) 10.47 (C-3), 30.26 (C-2), 55.23 (OCH$_3$), 71.93 (C-1), 110.47 (C-3′), 120.68 (C-5′), 127.4 (C-4′ or 6′), 128.10 (C-6′ or 4′), 132.59 (C-1′), 156.55 (C-2′) (found: M$^{+\cdot}$ 166.0995; calculated for $C_{10}H_{14}O_2$: 166.0994). The ee was determined by HPLC analysis using a Daicel Chiralcel OD column with 2.5% 2-propanol–hexane (flow rate 0.5 mL min$^{-1}$): (*S*)-1-(2-methoxyphenyl)-1-propanol 33.5 min, (*R*)-1-(2-methoxyphenyl)-1-propanol 35.5 min.

*4.9.5. 1-(2-Naphthyl)-1-propanol*

Off white solid (91.5 mg, 0.492 mmol, 49%) after purification by flash column chromatography (hexane:ethyl acetate, 78:22), mp 29–31°C: $\nu_{max}$ ($CCl_4$ soln.)/$cm^{-1}$ 3615 (OH), 3059, 855, 819; $\delta_H$ (270 MHz, $CDCl_3$) 0.89 (t, *J*=7.4, 3H, C*H*$_3$CH$_2$), 1.70–1.99 (m, 2H, CH$_3$C*H*$_2$), 2.33 (s, 1H, OH), 4.67 (t, *J*=6.6, 1H, H-1), 7.39–7.51 (m, 3H, ArH), 7.70 (s, 1H, H-1′), 7.76–7.81 (m, 3H, ArH); $\delta_C$ (68.7 MHz, $CDCl_3$) 10.30 (C-3), 31.89 (C-2), 76.20 (C-1), 124.32, 124.89, 126.02, 126.09, 127.83, 128.08, 128.35 (all ArC-H), 133.11, 133.4 (both ArC), 142.10 (C-2′) (found: $M^{+\cdot}$ 186.1045; calculated for $C_{13}H_{14}O$: 186.1045). The ee was determined by HPLC analysis using a Daicel Chiralcel OD column with 4% 2-propanol–hexane (flow rate 1 mL $min^{-1}$): (*R*)-1-(2-naphthyl)-1-propanol 25.9 min, (*S*)-1-(2-naphthyl)-1-propanol 22.9 min.

*4.9.6. (*E*)-1-Phenyl-1-penten-3-ol*

Colourless oil (145.8 mg, 0.899 mmol, 90%) after purification by flash column chromatography (hexane:ethyl acetate, 74:26): $\nu_{max}$ (liq. film)/$cm^{-1}$ 3690–3100 (OH), 3026, 965, 748, 693; $\delta_H$ (270 MHz, $CDCl_3$) 0.93 (t, *J*=7.3, 3H, C*H*$_3$CH$_2$), 1.51–1.74 (m, 2H, CH$_3$C*H*$_2$), 2.53 (s, 1H, OH), 4.15 (q, *J*=6.8, 1H, H-3), 6.17 (dd, *J*=15.9, 6.8, 1H, H-2), 6.52 (d, *J*=15.9, 1H, H-1), 7.13–7.36 (m, 5H, ArH); $\delta_H$ (68.7 MHz, $CDCl_3$) 9.88 (C-5), 30.26 (C-4), 74.38 (C-3), 126.5, 127.64, 128.64, 130.38, 132.44 (all $sp^2$ C), 137.05 (C-1′) (found: $M^{+\cdot}$ 162.1030; calculated for $C_{11}H_{14}O$: 162.1045). The ee was determined by HPLC analysis using a Daicel Chiralcel OD column with 5% 2-propanol–hexane (flow rate 1 mL $min^{-1}$): (*R*,*E*)-1-phenyl-1-penten-3-ol 16.9 min, (*S*,*E*)-1-phenyl-1-penten-3-ol 27.2 min.

*4.9.7. 1-Phenyl-3-pentanol*

Colourless oil (112 mg, 0.682 mmol, 68%) after purification by flash column chromatography (hexane:ethyl acetate, 4:1): $\nu_{max}$ (liq. film)/$cm^{-1}$ 3700–3100 (OH), 3026, 746, 699; $\delta_H$ (270 MHz, $CDCl_3$) 0.92 (t, *J*=7.4, 3H, C*H*$_3$CH$_2$), 1.39–1.57 (m, 2H, CH$_3$C*H*$_2$), 1.69–1.84 (m, 2H, C-2 CH$_2$), 1.97 (s, 1H, OH), 2.59–2.84 (m, 2H, C-1 CH$_2$), 3.48–3.57 (m, 1H, H-3); $\delta_C$ (68.7 MHz, $CDCl_3$) 9.99 (C-5), 30.35 (C-4), 32.19 (C-2), 38.69 (C-1), 72.67 (C-3), 125.8 (C-4′), 128.54 (ArC-H), 142.40 (C-1′) (found: $M^{+\cdot}$ 164.1204; calculated for $C_{11}H_{16}O$: 164.1201). The ee was determined by HPLC analysis using a Daicel Chiralcel OD column with 5% 2-propanol–hexane (flow rate 1 mL $min^{-1}$): (*S*)-1-phenyl-3-pentanol 13.3 min, (*R*)-1-phenyl-3-pentanol 19.2 min.

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