Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 3461–3490

TETRAHEDRON: *ASYMMETRY*

Concepts for ligand design in asymmetric catalysis: a study of chiral amino thiol ligands

James C. Anderson,* Rachel Cubbon, Michael Harding and Daniel S. James

Department of Chemistry, University of Sheffield, Sheffield, S3 7HF, UK

Received 19 August 1998; accepted 26 August 1998

Abstract

A series of new chiral sulfur–nitrogen chelate ligands, derived from amino acids, has been synthesised rationally. Fruitless experiments into catalytic asymmetric conjugate additions and desymmetrisation of *meso*-epoxides led us to analyse our ligands in the catalytic asymmetric addition of diethylzinc to aromatic aldehydes. These latter experiments were successful with chiral benzylic alcohols being obtained in up to 82% enantiomeric excess.

1. Introduction

Successful asymmetric catalysis with metal complexes depends, in part, upon the steric and electronic properties of chiral ligands. We set out to design rationally some new chiral ligands for use in enantioselective conjugate additions of Grignard and diorganozinc reagents to α,β-unsaturated carbonyl systems, catalysed by copper and nickel salts. The best results in the field have been obtained with copper(I) catalysts when bound to a potentially bidentate chiral ligand containing a readily polarisable centre such as sulfur or more recently phosphorus.[1] We decided to begin our investigation by developing a new ligand system for copper catalysed reactions from amino acids and wanted to be able to determine the origins of chirality induction so as to provide a basis for further ligand design. We envisaged that amino acid derived amino alcohols could be transformed into amino thiols and that the sulfur substituent would, by analogy to other ligand systems in the literature,[1] render our copper–chiral ligand complex catalytically active. Chiral ligands derived from amino acids have been used extensively in asymmetric catalysis with varying degrees of success. We anticipated that a potentially stereogenic nitrogen donor atom could have beneficial effects on cuprate systems and other metal catalysed processes. In the design of our ligands, careful attention was paid to the notion that the chirality inherent to the backbone of the amino acid could be transmitted closer to the reaction centre by the correct choice of substituents

* Corresponding author. E-mail: j.anderson@sheffield.ac.uk

0957-4166/98/$ - see front matter
PII: S0957-4166(98)00344-9

on nitrogen. Upon chelation, a differentially substituted nitrogen atom could become stereogenic and transmit the stereoinducing power of the ligand closer to the metal centre (Fig. 1). An *N*,*N*-diphenylated nitrogen atom could also be rendered stereogenic through restricted rotation.[2]

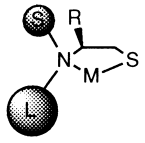


Fig. 1.

The first series of ligands (Fig. 2) were derived from L-valine and all contained potentially stereogenic nitrogen atoms. A comparison of thiol ligands **1** and **2** versus secondary amine ligands **3** and **4** would investigate the effect of the anion being centred on sulfur or nitrogen. The sulfonamide ligands **5** and **6** were prepared due to the precedent that achiral copper–sulfonamide complexes catalyse the addition of diorganozincs to enones.[3] Sulfonamide–oxygen chiral chelate ligands have been investigated in this context and have given moderate enantioselectivities.[4] A sulfur partner to the sulfonamide in a chiral chelate ligand may improve the reaction as sulfur has higher affinities towards zinc and copper than oxygen.

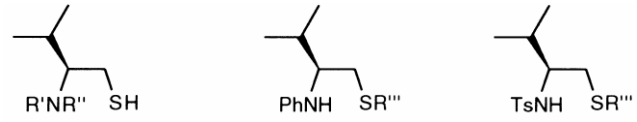
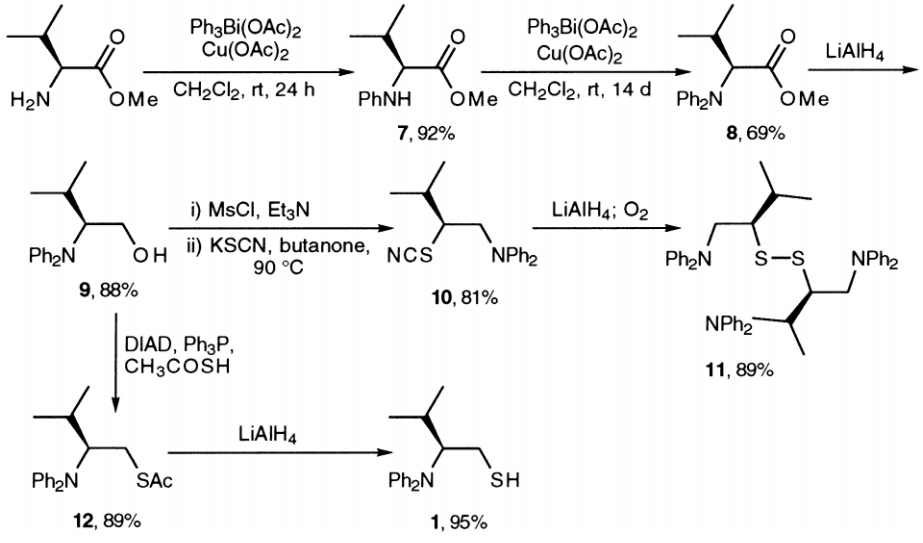


Fig. 2.

2. Synthesis of ligands

Treatment of (*S*)-valine methyl ester with triphenylbismuth diacetate[5] in the presence of catalytic copper(II) acetate (10 mol%)[6] gave the *N*-monophenylated ester **7** in good yield (92%, Scheme 1). Diphenylation of the nitrogen was most readily achieved by treatment of **7** with excess triphenylbismuth diacetate, which after 14 days gave **8** (69%). Palladium catalysed transformations,[7] in our hands, were unable to surpass the yield of *N*,*N*-diphenylated material obtained with the bismuth chemistry. The thiol group was introduced via the amino alcohol produced from lithium aluminium hydride reduction of **8** which proceeded without epimerisation in 88% yield.[8] The amino alcohol **9** was then mesylated under standard conditions and heated with potassium thiocyanate in butanone to give thiocyanate **10** (81%).[9] Treatment with a suspension of lithium aluminium hydride in refluxing ether/tetrahydrofuran gave a pungent colourless oil with spectroscopic data in agreement with the structure of **1**. However, exposure to air caused the sample to solidify. Recrystallisation from light petroleum afforded colourless crystals which were suitable for single crystal X-ray crystallographic analysis.[10] The result showed that the product was a disulfide, which was not unexpected, but with the chirality adjacent to sulfur not nitrogen (**11**, Fig. 3).

The diastereomerically pure disulfide **11** could be prepared by treatment of the crude reduced thiocyanate with oxygen in ethanol in 89% yield. Although we had hoped that the steric and electronic character of the *N*,*N*-diphenylated amine would prevent internal displacement of the mesylate, it is apparent that under the displacement reaction conditions, an intermediate aziridinium species is formed.



Scheme 1.

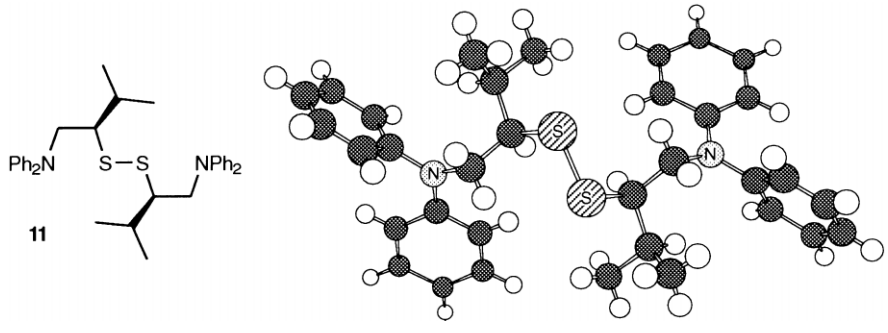
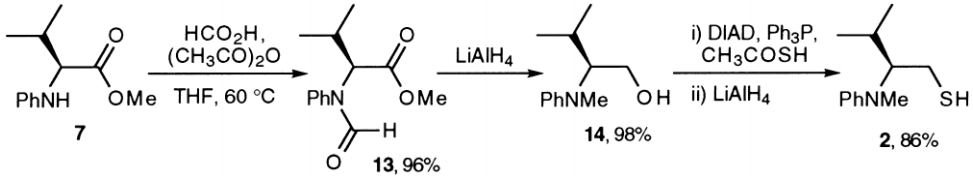


Fig. 3.

Thiocyanate attack then proceeds at the most reactive and sterically hindered centre. Rossiter has invoked this mechanism in the synthesis of piperidine containing (*R*,*R*)-DIMAPP ligands.[11] A different approach to the formation of ligand **1** had to be adopted. Following a procedure developed by Volante the amino alcohol was converted to the thiolacetate via a modified Mitsunobu reaction.[12] Treatment of **9** with thiolacetic acid in the presence of triphenylphosphine and diisopropylazodicarboxylate yielded the thiolacetate **12** in 89% yield which could be reduced with lithium aluminium hydride to give **1** (95%). Physical data for **1** were consistent with the molecular formula and the NMR spectrum was different to that of **11**.

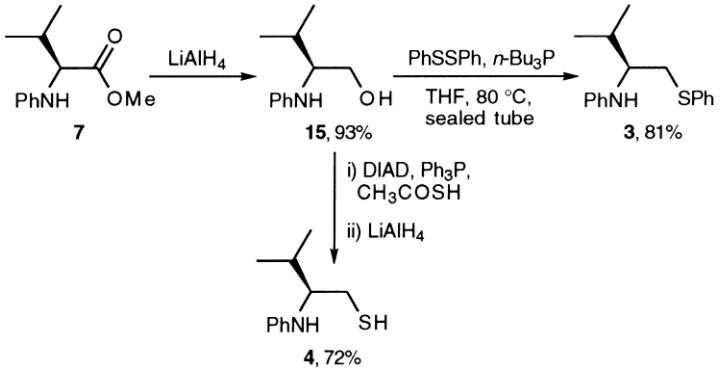
The *N*-methyl substituent of ligand **2** was introduced by formylation[13] as detailed in Scheme 2.



Scheme 2.

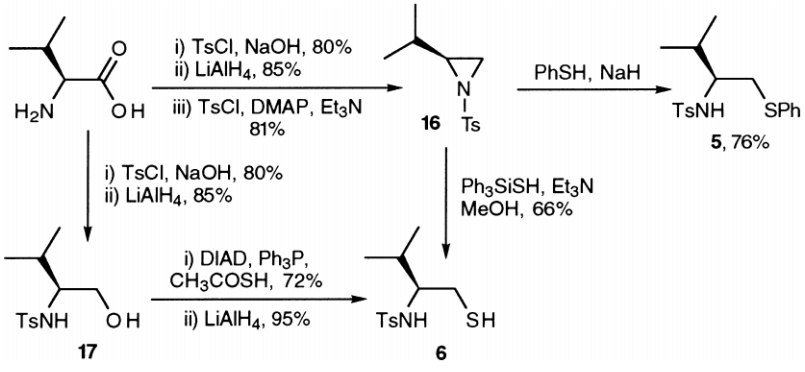
The secondary amine ligands **3** and **4** were synthesised from a common precursor **15** (Scheme 3), with the introduction of the phenylthioether achieved by heating in a sealed tube with tri-*n*-butylphosphine

and diphenyldisulfide in THF for 72 hours[14] to give **3** (81%). Introduction of the thiol group for ligand **4** followed the standard Mitsunobu/reduction procedure. The intermediate thiolacetate formed from **15** in 82% yield was unstable for prolonged periods of time at room temperature, undergoing an intramolecular cyclisation to the thiazolium ion.



Scheme 3.

Sulfonamide ligands **5** and **6** were synthesised from the known *N*-tosyl aziridine **16** derived from (*S*)-valine (Scheme 4).[15] Treatment of **16** with sodium phenylthiolate via a similar procedure used for the regiospecific opening of bis-aziridines,[16] furnished ligand **5** in 76% yield.



Scheme 4.

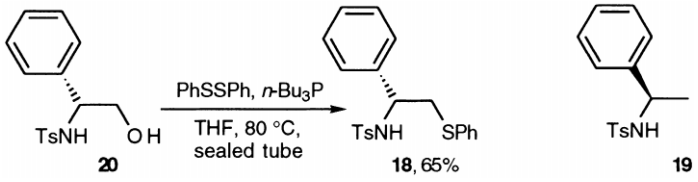
Treatment of **16** with sodium hydrosulfide gave only moderate yields (~50%) of the desired *N*-tosylamino thiol **6**, despite quantitative yields being realised in analogous reactions on similar substrates.[16] As triphenylsilylthiol[17] can be used to form β-hydroxymercaptans from epoxides[18] we envisaged that treatment of **16** with this reagent should furnish our desired β-*N*-tosylamino mercaptan **6**. Treatment of **16** with a solution of triphenylsilylthiol in methanol in the presence of triethylamine gave **6** in a modest 66% yield. A more reliable procedure involved treatment of **17** under the standard Mitsunobu/reduction conditions.

3. Conjugate addition and desymmetrisation experiments

In order to assay our ligands in conjugate addition reactions we chose to study the copper-catalysed addition of *n*-butylmagnesium chloride to cyclohexanone as we believed this system would be sensitive enough to indicate any activity. Although catalytic quantities of our copper–chiral ligand mixtures displayed higher chemical yields of selective 1,4-addition product than the system employing only metal

salt, none achieved any useful level of asymmetric induction,[19] despite the use of additives such as HMPA[20,21] and silyl chlorides[21] to maximise enantioselection. In an attempt to prepare a heterocuprate reagent, stoichiometric quantities of ligands **1** and **2** with copper(I) iodide were employed. Under identical conditions to those used for the catalytic system very low chemical yields were obtained (5 and 6% respectively) which suggested the formation of an unreactive heterocuprate (*vide infra*).

Due to our disappointing results above we investigated the ability of ligands **2**, **5** and **18** to effect the copper(I) catalysed addition of diethylzinc to cyclohexen-1-one.[22] Ligand **18** is structurally very similar to **19**, one of the best chiral sulfonamides in the literature for this reaction, and was synthesised in analogous fashion to ligand **5** from the known *N*-tosylamino alcohol **20** (Scheme 5).[23]



Scheme 5.

Catalytic quantities of ligand **18** and copper(I) cyanide delivered the highest chemical yield of 66%, but with no enantioinduction. It is plausible that chelation of the ligand to copper through nitrogen and sulfone oxygen, as postulated by Noyori,[3] may render the chiral substituent too far from the reactive centre making it ineffective in transmitting its stereochemical information to the reaction sphere. However, our result was surprising when compared to the moderate enantioselectivities obtained with the structurally similar chiral sulfonamide **19** and suggested that the additional sulfide substituent is detrimental to enantioinduction. Based upon literature precedent[24,25] we attempted the nickel(II) catalysed addition of diethylzinc to enones in the presence of the hydroxy analogues of ligands **1** and **2**, which are our synthetic precursors to these ligands, **9** and **14** respectively. Unfortunately only moderate yields and no meaningful enantioinductions were observed.

During the latter half of this work we also endeavoured to use these ligands to effect the asymmetric nucleophilic ring opening of *meso*-epoxides. We assayed the effectiveness of chiral ligands **1**–**6** with copper(I) iodide at catalysing the addition of *iso*-butylmagnesium bromide to cyclohexene oxide. Only ligands bearing a thiol substituent gave any yield of product and none higher than the control reaction performed with no ligand (67%). All products were virtually racemic. Stoichiometric experiments performed with heterocuprate species derived from ligands **1** and **4** (1 molar equivalent each of deprotonated ligand, copper(I) iodide and *i*-BuMgCl) gave no product at all. This result was similar to that observed in our conjugate addition experiments where only very low yields of addition product were obtained with stoichiometric cuprate reagents derived from ligands **1** and **2**. These results suggest that the heterocuprate presumably obtained in the stoichiometric experiment is unreactive. In the catalytic experiments the excess of Grignard reagent may force the formation of a more reactive homocuprate via the equilibrium outlined in Eq. 1.

$$\underset{\text{heterocuprate}}{RCu(L^*)MgCl} + RMgCl \rightleftharpoons \underset{\text{homocuprate}}{R_2CuMgCl} + L^*MgCl \quad (1)$$

However conjugate addition experiments employing only catalytic copper iodide also gave only low yields of addition product, despite the possibility that a homocuprate reagent would had been formed. This anomalous observation may serve to highlight the mechanistic differences between the two copper catalysed reactions we have investigated.

On the whole it would seem that our ligands produce unreactive chiral heterocuprate species, despite possessing features prominent in successful chiral ligands used with copper in the literature. After this disappointing, but illuminating, foray we turned our attention to other metal centred catalytic processes which could be made enantioselective with our chiral N,S-chelate ligands.

4. Asymmetric catalytic addition of diethylzinc to aromatic aldehydes

One of the most promising classes of chiral ligands for the catalytic asymmetric addition of diorganozincs to aldehydes are the amino thiols. The corresponding zinc thiolate catalysts have displayed enhanced reactivity and selectivity over their alcohol counterparts. This superior catalytic activity is thought to arise from numerous factors:[26] (i) the thiol is more polarisable compared to the oxygen in alcohols; (ii) the thiol and thiolates have a higher affinity towards metals, especially zinc; and (iii) the metal thiolates have less tendency to diminish the Lewis acidity of a metal compared to metal alcoholates. The success and structural diversity of these ligands are illustrated in Fig. 4 with respect to the addition of diethylzinc to benzaldehyde.[27]

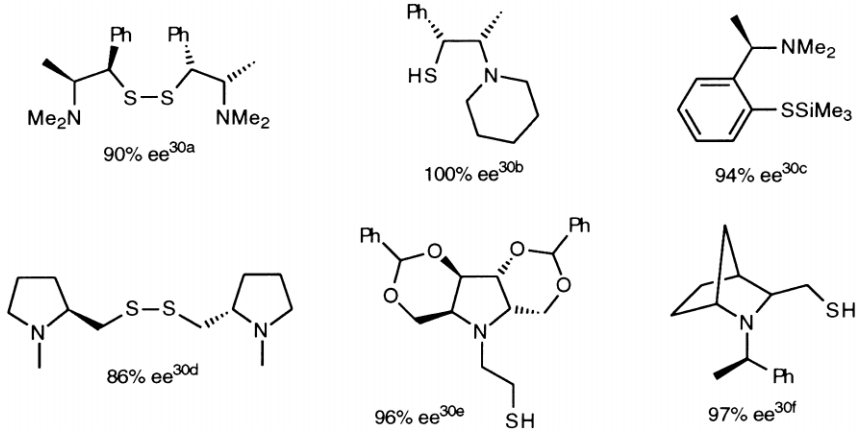
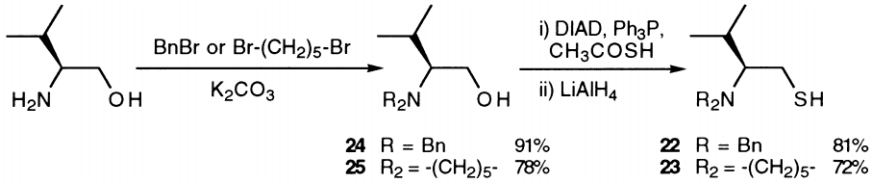


Fig. 4.

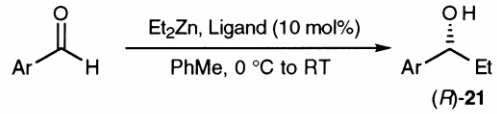
Preliminary attempts to produce optically active secondary alcohols **21** via the addition of diethylzinc to aromatic aldehydes employed ligands **1** and **2** (Table 1). Good yields of secondary alcohols were obtained. Ligand **2** gave consistently higher levels of enantiomeric excess[28] than ligand **1**, with both giving (*R*)-**21**.[29] In some ligand systems the use of lithiated ligand has had a positive effect on enantioselection.[30] The use of lithiated **1** and **2** in this reaction had a detrimental effect on enantioselection.



Scheme 6.

To determine whether the potential of ligands **1** and **2** to possess a stereogenic nitrogen influences the level of enantioselectivity we chose to synthesise ligands **22** and **23**, both of which possess symmetrical nitrogen substituents (Scheme 6).

Table 1
Ligand catalysed additions of diethylzinc to aromatic aldehydes



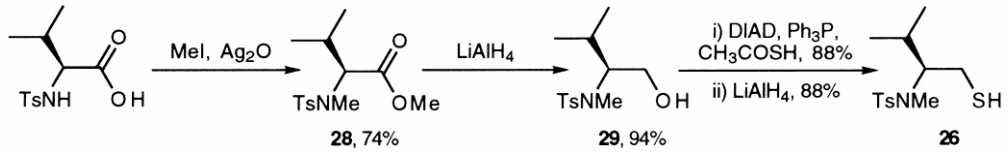
Entry	Ligand	Ar	Time/h	Yield **25**/%[a]	ee/%[32]
1	**1**	Ph	20	85	74
2	**1**	*o*-$MeOC_6H_4$	20	88	52
3	**1**	*p*-$MeOC_6H_4$	40	91	62
4	**1**	*p*-MeC_6H_4	20	75	62
5	**1**	*p*-ClC_6H_4	20	56	75
6	**2**	Ph	8	89	82
7	**2**	*o*-$MeOC_6H_4$	8	83	79
8	**2**	*p*-$MeOC_6H_4$	8	90	78
9	**2**	*p*-MeC_6H_4	8	80	81
10	**2**	*p*-ClC_6H_4	8	86	81
11	Li-**1**	Ph	20	85	66
12	Li-**2**	Ph	12	90	76
13	**22**	Ph	20	86	55
14	**22**	*o*-$MeOC_6H_4$	20	78	44
15	**22**	*p*-$MeOC_6H_4$	20	73	43
16	**22**	*p*-MeC_6H_4	20	79	53
17	**22**	*p*-ClC_6H_4	20	98	44
18	**23**	Ph	4	78	66
19	**23**	*o*-$MeOC_6H_4$	4	92	65
20	**23**	*p*-$MeOC_6H_4$	12	100	62
21	**23**	*p*-MeC_6H_4	6	78	66
22	**23**	*p*-ClC_6H_4	4	87	70

[a]Isolated yields of pure products.

Alkylation of L-valinol with benzylbromide or 1,5-dibromopentane gave the amino alcohols **24** and **25**. Introduction of the thiol substituent using the Mitsunobu/reduction procedure gave ligands **22** and **23** in good overall yields.

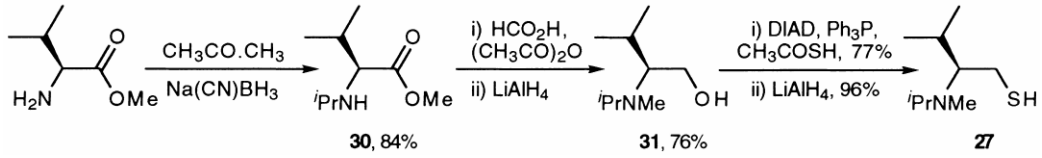
Under the standard addition conditions, both ligands that possess symmetrical nitrogen substituents did not perform as well as ligand **2** (compare entries 6–10 for **2** with 13–17 for **26** and 18–22 for **27**). These results suggest that giving the nitrogen atom the potential to become stereogenic leads to enhanced enantioselection.

To extend this work to other ligands possessing potentially stereogenic nitrogen donors, we synthesised ligands **26** and **27** (Schemes 7 and 8 respectively). Both of these potential catalysts are structural analogues of **2**, possessing a nitrogen substituted with a methyl group and a tosyl (**26**) or *iso*-propyl group (**27**). These studies would allow us to compare electronically and structurally different catalysts and hopefully provide insight into further ligand design. Ligand **26** was prepared from *N*-tosyl L-valine[15] by bis-methylation (74%), reduction (94%) and then introduction of the thiol substituent using the Mitsunobu/reduction procedure (77%).



Scheme 7.

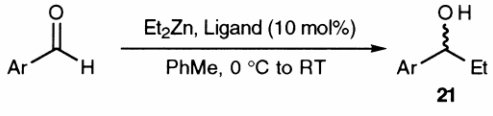
The introduction of the *iso*-propyl substituent was achieved following a modified literature procedure.[31] Treatment of L-valine methyl ester with acetone and sodium cyanoborohydride in ethanol gave the *N*-*iso*-propyl L-valine methyl ester **30** in 84% yield. Introduction of the *N*-methyl substituent and thiol function was achieved in a similar manner as for the synthesis of ligand **2** (Scheme 8).



Scheme 8.

In diethylzinc additions to aromatic aldehydes catalysed by ligands **26** and **27**, good chemical yields were obtained (Table 2) although longer reaction times were needed for the *N*-tosyl ligand (entries 1–5). The *N*-tosyl ligand **26** not only gave very low enantioselectivity, but also selected the (*S*)-enantiomer of **21**. The enantioselectivities obtained with ligand **27** (entries 6–10) were far superior to those with **26** (entries 1–5). In all of the additions catalysed by **27**, (*R*)-**21** was obtained in good chemical and optical yield (ees>70%). Although this ligand performed consistently better than *N*,*N*-diphenyl amino thiol **1** it provided inferior results to the *N*-methyl-*N*-phenylamino thiol ligand **2** (compare Table 1, entries 1–10). It would seem that the coordinating ability of the lone pair may affect the rate of the reaction and the steric bulk around nitrogen may affect the enantioselection [compare results of ligands **1** and **2** (Table 5) and **30** and **31** (Table 2)].

Table 2
Ligand (RNMe) catalysed additions of diethylzinc to aromatic aldehydes



Entry	Ligand	Ar	Time/h	Yield **25**/%[a]	ee/%[32]
1	**26**	Ph	40	80	5 (*S*)
2	**26**	*o*-$MeOC_6H_4$	40	84	2 (*S*)
3	**26**	*p*-$MeOC_6H_4$	40	75	2 (*S*)
4	**26**	*p*-MeC_6H_4	40	77	4 (*S*)
5	**26**	*p*-ClC_6H_4	40	81	2 (*S*)
6	**27**	Ph	20	81	72 (*R*)
7	**27**	*o*-$MeOC_6H_4$	20	87	72 (*R*)
8	**27**	*p*-$MeOC_6H_4$	20	84	70 (*R*)
9	**27**	*p*-MeC_6H_4	20	85	72 (*R*)
10	**27**	*p*-ClC_6H_4	20	83	74 (*R*)

[a]Isolated yields of pure products.

By analogy to Kang's work[26] the sense of enantioselection may be explained by considering the ternary complexes **A** and **B** (Fig. 5, nitrogen substituents omitted for clarity). Transition state structure **A** is favoured over **B** due to the avoidance of a destabilising 1,3 interaction between diethylzinc* and the *iso*-propyl group. It is clear from the results that making the nitrogen chiral increases the enantioselectivity of our ligands. However a reason to account for this increase is not obvious.

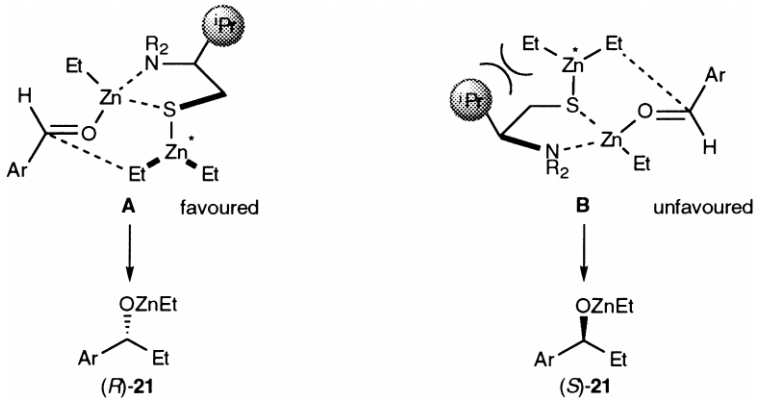


Fig. 5.

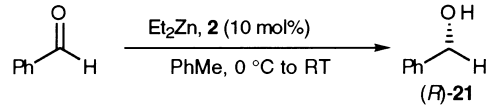
Upon chelation of the ligand to the zinc atom the smaller nitrogen substituent should occupy the top face of the chelate and the larger nitrogen substituent the bottom, thus avoiding interactions with the chiral group. As the larger nitrogen substituent increases in steric bulk: Bn, ^{i}Pr, Ph (ligands **22**, **27**, **2** respectively), their enantioselection with benzaldehyde increases 55 to 72 to 82% ee respectively. One could imagine that a serious effect of bulking up the underside of the ring would be to destabilise ternary structure **A** (due to a 1,3-steric interaction between the N-β substituent and diethylzinc*) with respect to ternary structure **B**. This would have the effect of reducing enantioselection with increasing steric bulk of the larger nitrogen substituent. The reason for an increase in enantioselectivity, in these experiments, with increasing steric bulk of the larger nitrogen substituent is not apparent and awaits further investigations. The dramatic erosion of enantioselectivity with the *N*-tosyl ligands may be attributed to the zinc atom coordinating to the oxygen of the sulfone. The chiral centre would then be further away from the reaction centre and have less of an impact on the stereochemical course of the reaction.

The rate of reaction with **2** generally surpassed that observed with ligand **1**. This may be attributed to the different electronic environments of the amine groups with the lone pair of *N*,*N*-diphenylamine being less available for coordination to the metal centre than that of the *N*-phenyl-*N*-methylamine. To assess how quickly ligand **2** catalysed the addition of diethylzinc to benzaldehyde the reaction was quenched after set times and the quantity and enantiopurity of (*R*)-phenylpropanol measured (Table 3). Although there is a drop in the isolated yield of (*R*)-**21** with decrease in reaction time, the extent of enantioselection is independent. Four hours represents a competitive reaction time in comparison to other reported catalytic systems.[27]

The catalytic efficiency of ligand **2** was then examined. The results (Table 4) indicate that the ligand is equally effective at very low levels of catalyst loading. The observed chemical yields and enantiomeric excesses did not alter upon reducing the amount of catalyst from 10 to 1 mol% (compare entries 1 and 4). This lack of response of the enantiomeric excess to changes in the benzaldehyde/catalyst ratio is in stark contrast to results described for amino alcohol ephedrine derivatives[32] and suggests complete formation of the active catalyst rather than an equilibrium between the catalyst and its components.[33]

Many of the established ligands used to catalyse the addition of diorganozincs to aldehydes are

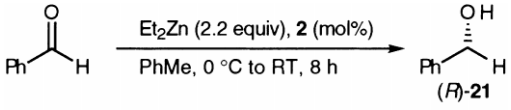
Table 3
Effect of reaction time upon ligand **2** catalysed additions of diethylzinc to benzaldehyde



Entry	Time/h	Yield **25**/%[a]	ee/%[32]
1	8	89	80
2	4	90	82
3	2	71	81
4	1	58	82
5	0.5	48	82

[a]Isolated yields of pure products.

Table 4
Effects of catalyst loading upon ligand **2** catalysed diethylzinc additions to benzaldehyde



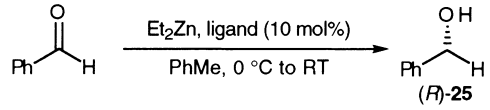
Entry	mol%	Yield **25**/%[a]	ee/%[32]
1	10	89	80
2	5	90	82
3	2.5	90	81
4	1	92	80

[a]Isolated yields of pure products.

substituted amino alcohols. To assess the importance of the thiolate in effecting an efficient conversion we compared the reactivity of some of our amino thiol ligands **1**, **2** and **22** with their amino alcohol precursors **9**, **14** and **24**. We found that in additions of diethylzinc to benzaldehyde our thiol ligands provided far superior results over their hydroxyl analogues (Table 5). All of the reactions involving amino thiol ligands were characterised by greater reaction rates and higher levels of enantioinduction which supports the conclusions of Kang et al.[26] Of the amino-alcohol ligands, **14**, the hydroxyl analogue of our most effective ligand **2**, afforded the best results. This further supports our observation that the potentially stereogenic *N*-methyl-*N*-phenylamino group can play an instrumental role in the transfer of stereochemical information.

Kellogg has employed disulfides, produced by the oxidation of ephedrine derived thiols, in the addition of diethylzinc to benzaldehyde. These ligands have been shown to be very effective catalysts.[35] The results obtained surpassed those obtained with the free thiols. During our investigations into amino-thiol catalysed additions we recovered our ligands in high yields (>80%) as the disulfides (**32**–**34**, Fig. 6). They could also be prepared by oxidation of the requisite monomers with oxygen. We employed all of the ligands in Fig. 6 as catalysts in the asymmetric ethylation of benzaldehyde. The chiral disulfide **11** formed during our preliminary investigations into the synthesis of ligand **1** was also analysed. Possessing a chiral centre adjacent to the sulfur, this would provide an interesting analysis of the effect this chiral centre had upon enantioinduction in the reaction. As the disulfide is believed to be converted to the

Table 5
Comparison of thiolate and alcoholate ligand catalysed diethylzinc additions to benzaldehyde



Entry	Ligand	Time/h	Yield **25**/%[a]	ee/%[32]
1	**1**	20	85	74
2	**9**	48	42	31
3	**2**	4	90	82
4	**14**	48	70	52
5	**22**	12	90	58
6	**24**	48	79	42

[a]Isolated yields of pure products.

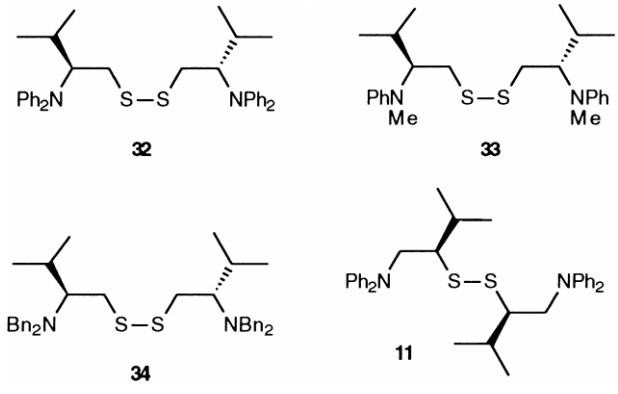
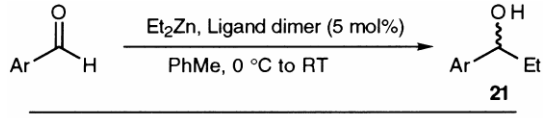


Fig. 6.

Table 6
Comparison of thiolate and disulfide derived catalysts upon the addition of diethylzinc to benzaldehyde



Entry	Ligand	Time/h	Yield **25**/%[a]	ee/%[32]
1	**1**	20	85	74 (*R*)
2	**32**	48	67	59 (*R*)
3	**2**	4	90	82 (*R*)
4	**33**	48	85	80 (*R*)
5	**22**	12	90	58 (*R*)
6	**34**	48	76	38 (*R*)
7	**11**	48	75	25 (*S*)

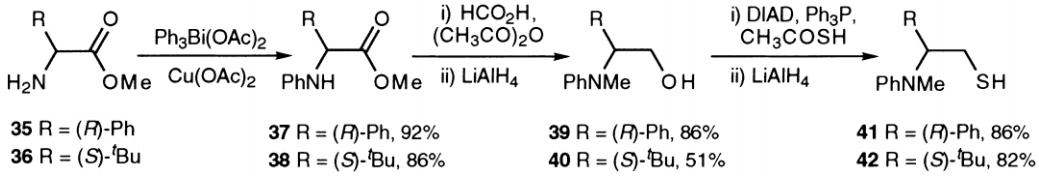
[a]Isolated yields of pure products.

thiolate and thiol[33] upon addition of diethylzinc the reactivity of 5 mol% of the disulfide was compared against 10 mol% of the free thiol (Table 6).

Contrary to reports by Kellogg the disulfide analogues were generally inferior catalysts when compared to the amino-thiol ligands. Our findings were more in line with the observations made by Kang et al.[26] who reported increases in reaction time and decreases in enantioselectivities with their disulfide counterparts. However, the enantioselectivities obtained with disulfide **33** (80% ee) paralleled very well those obtained with the free thiol **2** (82% ee). Although the reaction time with the disulfide was definitely longer than that with the thiol, the disulfide benefits from increased stability. Consequently, with some sacrifice in terms of reaction time and negligible difference in enantioselectivity the disulfide **33** is a very attractive reagent.

The chiral disulfide **11** possessing a chiral centre adjacent to the sulfur produced the (*S*)-enantiomer of the secondary alcohol, opposite to that obtained using its structural isomer **32**. This is in disagreement with the configurational rules proposed by Noyori for β-amino alcohols.[34] The reason for this reversal of enantioselection is not clear to us at present and is surprising given that N,S-chelates derived from norephedrine, which have two stereogenic centres blocking the same face of the catalyst, give better enantioselectivities than any of our ligands.[27b,35] In these latter ligands we assumed that the stereoinducing effect of the stereogenic centre adjacent to nitrogen was reinforced by the stereocentre adjacent to sulfur. Our results for ligand **11** now shed doubt on this assumption and maybe on the whole accepted pictorial view of how N,S-chelate ligands control enantioselection in these types of reaction.

The final factor governing enantioselection concerned the bulk of the chiral group on the backbone of the chelate ligand. We chose to analyse the *N*-methyl-*N*-phenylamino thiol ligands derived from (*R*)-phenylglycine and (*S*)-*tert*-leucine and compare them with ligand **2** derived from L-valine. The ligands were prepared in an analogous fashion to **2**. Starting from the amino acid methyl esters **35** and **36**, ligands **41** and **42** were prepared respectively following the sequence of mono-*N*-phenylation, methylation via the formamide and introduction of the thiol function by the Mitsunobu/reduction protocol (Scheme 9).

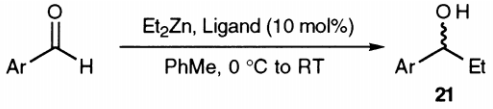


Scheme 9.

Ligands **41** and **42** were used to catalyse the addition of diethylzinc to various aromatic aldehydes and the results are summarised in Table 7.

The phenylglycine derived ligand **41** generated good chemical yields of the corresponding secondary alcohols (entries 4–6). In all of the cases studied, the (*S*)-enantiomer of the 1-arylpropanol was obtained which is in agreement with the configurational rules proposed by Noyori for β-amino alcohols.[36] Consistently good levels of enantioinduction were observed in the additions, though slightly lower than those obtained with ligand **2**. Ligand **42** possessing the sterically demanding *tert*-butyl group was a less effective catalyst. Although good chemical yields were obtained reaction times were generally longer and the levels of enantioinduction were well below those obtained with ligands **2** and **41**. Presumably the bulky *tert*-butyl group causes severe steric compression in the desired transition state which has a detrimental effect upon enantioselectivity. This has been observed in numerous other ligand-catalysed systems.[37]

Table 7
Comparison of catalysts of PhNMe ligands derived from L-valine, (*R*)-phenylglycine and (*S*)-*tert*-leucine



21

Entry	Ligand	Ar	Time/h	Yield **25**/%[a]	ee/%[32]
1	**2**	Ph	8	89	82 (*R*)
2	**2**	*o*-$MeOC_6H_4$	8	83	79 (*R*)
3	**2**	*p*-$MeOC_6H_4$	8	90	78 (*R*)
4	**41**	Ph	8	90	69 (*S*)
5	**41**	*o*-$MeOC_6H_4$	8	87	72 (*S*)
6	**41**	*p*-$MeOC_6H_4$	40	89	65 (*S*)
7	**42**	Ph	24	80	48 (*R*)
8	**42**	*o*-$MeOC_6H_4$	24	74	12 (*R*)
9	**42**	*p*-$MeOC_6H_4$	40	77	1 (*R*)

[a]Isolated yields of pure products.

5. Conclusions

We have developed syntheses of a variety of new chiral N,S-chelate ligands, potentially available from each enantiomer of amino acids. The Mitsunobu/reduction procedure was found to be the best method for the synthesis of amino thiols from amino alcohols. These were assayed for chirality transfer in cuprate chemistry and as catalysts for the addition of diethylzinc to aromatic aldehydes. Despite chiral ligands **1**–**6** possessing many of the features prominent in successful ligands for cuprate chemistry, they were found to be poor chiral ligands and we believe our derived heterocuprates were less reactive than other species present in the reaction mixtures. Concurrent experiments also revealed the ligands were impotent in the nucleophilic desymmetrisation of *meso*-epoxides. Ligand **19**, structurally very similar to **20**, except for possessing a ligating sulfur substituent, disappointingly gave no enantioinduction in the copper-catalysed addition of diethylzinc to cyclohexenone.

Our ligands were effective for the asymmetric catalysed addition of diethylzinc to aromatic aldehydes and the results, although not the best in the field, do support our hypothesis that a potentially stereogenic nitrogen atom can exert more efficient enantioinduction. Our most efficient amino-thiol ligand **2** delivered (*R*)-phenylpropanol in 82% ee in a reaction time of 4 hours. As little as 1 mol% of ligand was efficient. A disubstituted *N*-methyl-*N*-phenyl nitrogen donor seems to be important with potentially chiral nitrogen donors; *N*,*N*-diphenyl, *N*-*iso*-propyl-*N*-methyl and *N*-methyl-*N*-*para*-toluenesulfonyl proving less effective. Ligands derived from valine were the most efficient. A realistic transition state model eludes us at present as the accepted model cannot explain the increase in enantioselectivity gained from a potentially stereogenic nitrogen donor atom. We have also verified that our amino-thiols are more efficient than their disulfide precursors or their corresponding amino-alcohols. We are using the lessons from this study to develop second generation ligands for other metal-catalysed processes with a view towards understanding the principles of chirality transfer in asymmetric reactions.

6. Experimental

Our general experimental details have been reported.[38] Commercial copper(I) iodide was purified before use.[39]

6.1. *Methyl-(*S*)-[*N*-phenyl-2-amino-3-methyl]butanoate **7***

Triphenylbismuth diacetate (2.63 g, 4.72 mmol) and copper(II) diacetate (76 mg, 0.43 mmol) were added to a solution of L-valine methyl ester (562 mg, 4.29 mmol) in dichloromethane (50 ml). After being stirred at ambient temperature for 24 hours the reaction mixture was poured into water (100 ml) and extracted with dichloromethane (3×50 ml). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford a brown oil which was purified by flash column chromatography eluting with ethyl acetate/light petroleum (5%) to give **7** (813 mg, 92%) as a colourless liquid (found: C, 69.62; H, 8.24; N, 6.73; $C_{12}H_{17}O_2N$ requires C, 69.54; H, 8.27; N, 6.67%); $[\alpha]_D^{22}=-92$ (*c* 0.75, $CHCl_3$); ν_{max} (film)/cm^{-1} 3390 (NH), 1738 (C=O), 1603, 1507; δ_H (250 MHz; $CDCl_3$) 1.04 (3H, d, *J* 7.2, $CH(CH_3)_2$), 1.07 (3H, d, *J* 7.2, $CH(CH_3)_2$), 2.02–2.20 (1H, m, $CH(CH_3)_2$), 3.7 (3H, s, CO_2CH_3), 3.85 (1H, d, *J* 6.0, $CHCO_2Me$), 4.15 (1H, br s, –N*H*), 6.55–7.35 (5H, m, Ar); δ_C (63 MHz; $CDCl_3$), 18.7 ($CH(CH_3)_2$), 19.1 ($CH(CH_3)_2$), 31.6 ($CH(CH_3)_2$), 51.8 (CO_2CH_3)), 62.4 ($CHCH(CH_3)_2$), 113.5 (Ar), 118.2 (Ar), 129.3 (Ar), 146.2 (Ar), 175.5 (C=O); *m/z* (EI) 207 (M^+, 44%), 164 (52), 148 (100), 132 (13), 104 (55), 77 (29). (Found: M^+, 207.1258. $C_{12}H_{17}NO_2$ requires *M*, 207.1259.)

6.2. *Methyl-(*S*)-[*N,N*-diphenyl-2-amino-3-methyl]butanoate **8***

Triphenylbismuth diacetate (17.4 g, 10 mmol) and copper diacetate (0.19 g, 1 mmol) were added to a solution of **7** (2.15 g, 10 mmol) in dichloromethane (50 ml). After being left to stir at room temperature for 14 days the precipitates were filtered through Celite®, removal of the solvent *in vacuo* and purification by flash column chromatography eluting with ethyl acetate/light petroleum (2%) gave **8** (2.05 g, 69%) as a white solid, mp 32–33°C (ethyl acetate/light petroleum) (found: C, 75.92; H, 7.56; N, 4.67; $C_{18}H_{21}O_2N$ requires C, 76.30; H, 7.47; N, 4.94%); $[\alpha]_D^{22}=-95$ (*c* 0.8, $CHCl_3$); ν_{max} (film)/cm^{-1} 2962, 1740 (C=O), 1590, 1496; δ_H (250 MHz; $CDCl_3$) 0.89 (3H, d, *J* 6.5, $CH(CH_3)_2$), 0.97 (3H, d, *J* 6.5, $CH(CH_3)_2$), 2.27–2.48 (1H, m, $CH(CH_3)_2$), 3.6 (3H, s, CO_2CH_3), 3.85 (1H, d, *J* 9.4, $CHCO_2Me$), 4.15 (1H, br s, –N*H*), 6.87–7.16 (10H, m, Ar); δ_C (63 MHz; $CDCl_3$), 20.4 (2×$CH(CH_3)_2$), 28.7 ($CH(CH_3)_2$), 51.6 (CO_2CH_3), 69.8 ($CHCH(CH_3)_2$), 122.2 (Ar), 122.7 (Ar), 128.7 (Ar), 129.2 (Ar–H), 172.8 (C=O); *m/z* (EI) 283 (M^+, 25%), 240 (35), 224 (100). (Found: M^+, 283.1573. $C_{12}H_{17}NO_2$ requires *M*, 283.1572.)

6.3. *(*S*)-*N,N*-Diphenyl-2-amino-3-methyl-butan-1-ol **9***

A solution of **8** (300 mg, 1.06 mmol) in tetrahydrofuran (30 ml) was added to a suspension of lithium aluminium hydride (81 mg, 2.12 mmol) in diethyl ether (15 ml) at 0°C. The reaction mixture was left to stir at ambient temperature for 30 minutes and quenched at 0°C upon careful addition of water (0.08 ml), aqueous sodium hydroxide (15% w/v, 0.08 ml) and water (0.24 ml). The resulting white suspension was filtered through a pad of Celite® and the residue washed with tetrahydrofuran (20 ml). The organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to yield a colourless oil which was purified by column chromatography on silica eluting with ethyl acetate/light petroleum (15%) to give **9** (270 mg, 100%) as a colourless oil (found: C, 80.12; H, 8.24; N, 5.51; $C_{17}H_{21}NO$ requires C, 79.96; H, 8.29; N, 5.49%); $[\alpha]_D^{22}=-90$ (*c* 0.4, $CHCl_3$); ν_{max} (film)/cm^{-1} 3414 (OH), 2924, 1589, 1496; δ_H (250 MHz; $CDCl_3$)

0.84 (3H, d, *J* 6.7, CH(C*H*$_3$)$_2$), 0.99 (3H, d, *J* 6.7, CH(C*H*$_3$)$_2$), 1.77–1.93 (1H, m, C*H*(CH$_3$)$_2$), 3.60 (1H, dd, *J* 11.3, 9.5, CHC*H*αHβ), 3.50–3.92 (2H, m, CHCHα*H*β and C*H*CH(CH$_3$)$_2$), 6.74–7.23 (5H, m, Ar); δ_C (63 MHz; CDCl$_3$), 20.3 (CH(*C*H$_3$)$_2$), 21.2 (CH(*C*H$_3$)$_2$), 29.7 (*C*H(CH$_3$)$_2$), 61.9 (*C*H$_2$OH), 68.1 (*C*HCH(CH$_3$)$_2$), 121.9 (Ar), 123.0 (Ar), 129.3 (Ar), 152.6 (Ar); *m/z* (CI) 256 (M$^+$, 100%), 224 (86), 212 (40), 169 (13). (Found: M$^+$, 256.1702. $C_{17}H_{22}NO$ requires *M*, 256.1701.)

6.4. (S)-N,N-*Diphenyl-2-amino-3-methyl-1-methanesulfonyloxybutane*

Methanesulfonyl chloride (0.03 ml, 0.39 mmol) was added dropwise to a solution of **9** (88 mg, 0.35 mmol) and triethylamine (0.07 ml, 0.51 mmol) in dichloromethane (5 ml) at −5°C. The solution was then stirred at ambient temperature for 30 minutes. TLC analysis indicated that no starting material was left and the reaction mixture was concentrated *in vacuo* to yield the crude product (141 mg) which was used directly without additional purification.

6.5. (S)-N,N-*Diphenyl-1-amino-3-methyl-2-thiocyanobutane* ***10***

Potassium thiocyanate (335 mg, 3.5 mmol) was added to a solution of crude mesylate (95 mg, 1 mmol) in butan-2-one (20 ml). The reaction mixture was heated at reflux under nitrogen for 12 hours. All volatiles were removed under reduced pressure and the residue was separated between dichloromethane (40 ml) and water (40 ml). The aqueous layer was extracted with dichloromethane (3×20 ml) and the organic layers were combined, dried (MgSO$_4$) and concentrated *in vacuo* to afford a brown oil. Purification of the residue by column chromatography on silica eluting with ethyl acetate/light petroleum (5%) gave **10** (78 mg, 82%) as a colourless oil; $[\alpha]_D^{22}$=−57.7 (*c* 2.2, CHCl$_3$); ν_{max} (film)/cm^{-1} 2151 (SCN), 1589, 1496; δ_H (250 MHz; CDCl$_3$) 0.76 (3H, d, *J* 6.9, CH(C*H*$_3$)$_2$), 1.07 (3H, d, *J* 6.9, CH(C*H*$_3$)$_2$), 2.25–2.39 (1H, m, C*H*(CH$_3$)$_2$), 3.45–3.57 (1H, m, C*H*CH(CH$_3$)$_2$), 3.89 (1H, dd, *J* 14.9, 8.2, CHC*H*αHβ), 4.09 (1H, dd, *J* 14.9, 6.4, CHCHα*H*β), 6.82–7.31 (10H, m, Ar); δ_C (63 MHz, CDCl$_3$), 18.1 (CH(*C*H$_3$)$_2$), 20.2 (CH(*C*H$_3$)$_2$), 29.7 (*C*H$_2$SCN), 30.3 (*C*H(CH$_3$)$_2$), 50.1 (*C*HCH(CH$_3$)$_2$), 121.5 (Ar), 122.5 (Ar), 123.1 (S*C*N), 129.6 (Ar), 147.7 (Ar); *m/z* (EI) 296 (M$^+$, 14%), 239 (100), 168 (57), 91 (22). (Found: M$^+$, 296.1351. $C_{18}H_{21}NO_2$ requires *M*, 296.1347.)

6.6. (S,S)-*Bis-(*N,N-*diphenyl-1-amino-3-methylbutane-1-)disulfide* ***11***

A solution of **10** (154 mg, 0.52 mmol) in tetrahydrofuran (10 ml) was added to a stirred suspension of lithium aluminium hydride (79 mg, 2.08 mmol) in tetrahydrofuran (7 ml) at 0°C. The reaction mixture was heated to reflux for 30 minutes before being quenched at 0°C by careful addition of water (0.08 ml), aqueous sodium hydroxide (15% w/v, 0.08 ml) and water (0.24 ml). The resulting white suspension was filtered through a pad of Celite™ and the white solid residue washed with tetrahydrofuran (10 ml). The organic layers were dried (MgSO$_4$) and concentrated *in vacuo* to yield a colourless oil. The product was dissolved in ethanol and oxygen was bubbled through for 15 minutes. The solution was evaporated to dryness and purified by column chromatography on silica eluting with ethyl acetate/light petroleum (10%) to afford **11** (110 mg, 78%) as an amorphous white solid, mp 108–110°C (light petroleum) (found: C, 75.82; H, 7.63; N, 5.19; S, 11.93; $C_{34}H_{40}N_2S_2$ requires C, 75.51; H, 7.45; N, 5.18; S, 11.86%); $[\alpha]_D^{22}$=+136.7 (*c* 0.6, CHCl$_3$) ν_{max} (film)/cm^{-1} 1588, 1495; δ_H (250 MHz; CDCl$_3$) 0.76 (6H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 0.81 (6H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 2.12–2.28 (2H, m, C*H*(CH$_3$)$_2$), 3.01–3.10 (2H, m, C*H*CH(CH$_3$)$_2$), 3.88–4.07 (4H, m, C*H*$_2$N), 6.85–7.32 (20H, m, Ar); δ_C (63 MHz, CDCl$_3$) 17.1 (CH(*C*H$_3$)$_2$), 20.9 (CH(*C*H$_3$)$_2$), 28.4 (*C*H(CH$_3$)$_2$), 54.8 (*C*H$_2$N), 58.4 (*C*HCH(CH$_3$)$_2$), 121.3 (Ar), 121.6

(Ar), 129.3 (Ar), 148.3 (Ar); *m/z* (CI) 541 (M^+, 6%), 272 (100), 238 (29), 182 (78), 170 (15). (Found: M^+, 540.2637. $C_{34}H_{40}N_2S_2$ requires *M*, 540.2633.)

6.7. (S)-N,N-*Diphenyl-2-amino-3-methyl-1-thiolacetylbutane* ***12***

Diisopropyl azodicarboxylate (1.90 g, 9.4 mmol) was added to a well stirred solution of triphenylphosphine (2.46 g, 9.4 mmol) in tetrahydrofuran (50 ml) at 0°C.The reaction mixture became a creamy white suspension and was left to stir for a further 30 minutes before **9** (1.2 g, 4.7 mmol) and thiolacetic acid (0.67 ml, 9.4 mmol) were added simultaneously over 5 minutes. The reaction mixture was left to stir for 1 hour at 0°C. The resulting homogeneous yellow solution was concentrated *in vacuo* to afford a yellow oil. Purification of the residue by column chromatography on silica eluting with ethyl acetate/light petroleum (2.5%) gave **12** (1.29 g, 89%) as a colourless oil (found: C, 72.81; H, 7.65; N, 4.36; S, 10.11; $C_{19}H_{23}ONS$ requires C, 72.81; H, 7.4; N, 4.47; S, 10.21%); $[\alpha]_D^{22}=-40$ (*c* 0.5, $CHCl_3$); ν_{max} (film)/cm^{-1} 1690s (C=O), 1589s, 1495s; δ_H (250 MHz; $CDCl_3$) 1.05 (3H, d, *J* 6.7, $CH(CH_3)_2$), 1.08 (3H, d, *J* 6.7, $CH(CH_3)_2$), 1.94–2.12 (1H, m, $CH(CH_3)_2$), 2.29 (3H, s, $SCOCH_3$), 2.77 (1H, dd, *J* 13.8, 11.6, $CHCH\alpha H\beta$), 3.55 (1H, dd, *J* 13.8, 4.4, $CHCH\alpha H\beta$), 3.98 (1H, ddd, *J* 11.6, 10.2, 4.4, $CHCH(CH_3)_2$), 6.90–7.27 (10H, m, Ar); δ_C (63 MHz; $CDCl_3$) 20.7 ($CH(CH_3)_2$), 21.3 ($CH(CH_3)_2$), 30.6 ($CH(CH_3)_2$), 31.5 (CH_2S), 34.1 ($SCOCH_3$), 65.1 ($CHCH(CH_3)_2$), 121.7 (Ar), 123.0 (Ar), 129.2 (Ar), 147.6 (Ar), 196.3 (C=O); *m/z* (EI) 313 (M^+, 20%), 270 (87), 228 (12), 224 (100), 194 (15), 167 (13), 104 (13), 77 (16). (Found: M^+, 313.1490. $C_{19}H_{23}NOS$ requires *M*, 313.1500.)

6.8. (S)-N,N-*Diphenyl-2-amino-3-methylbutane-1-thiol* ***1***

A solution of **12** (200 mg, 0.64 mmol) in tetrahydrofuran (7 ml) was added to a stirred suspension of lithium aluminium hydride (98 mg, 2.56 mmol) at 0°C in tetrahydrofuran (6 ml). The reaction mixture was left to stir at ambient temperature for 10 minutes and quenched at 0°C by careful addition of water (0.1 ml), aqueous sodium hydroxide (15% w/v, 0.1 ml) and water (0.3 ml). The resulting white suspension was filtered through a pad of Celite® and the white solid residue washed with tetrahydrofuran (10 ml). The organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to yield a colourless oil which was purified by column chromatography on silica eluting with ethyl acetate/light petroleum (1.5%) to afford **1** (165 mg, 95%) as a colourless oil; $[\alpha]_D^{22}=-193.6$ (*c* 2.9, $CHCl_3$); ν_{max} (film)/cm^{-1} 2960, 2570 (SH), 1589, 1494; δ_H (250 MHz; $CDCl_3$) 0.98 (3H, d, *J* 6.7, $CH(CH_3)_2$), 1.05 (3H, d, *J* 6.7, $CH(CH_3)_2$), 1.5 (1H, dd, *J* 8.5, 7.0, SH), 1.92–2.09 (1H, m, $CH(CH_3)_2$), 2.77–2.86 (1H, m, CH_2SH), 3.86–3.98 (1H, m, $CHCH(CH_3)_2$), 6.91–7.29 (5H, m, Ar); δ_C (63 MHz; $CDCl_3$) 21.1 ($CH(CH_3)_2$), 21.4 ($CH(CH_3)_2$), 26.2 (CH_2SH), 34.2 ($CH(CH_3)_2$), 69.8 ($CHCH(CH_3)_2$), 121.8 (Ar), 123.0 (Ar), 129.2 (Ar), 148.1 (Ar); *m/z* (CI) 271 (M^+, 39%), 228 (73), 224 (100), 194 (19), 169 (19), 148 (16), 104 (16), 77 (15). (Found: M^+, 271.1395. $C_{17}H_{21}NS$ requires *M*, 271.1395.)

6.9. *Methyl (S)-[N-formyl-N-phenyl-2-amino-3-methyl]butanoate* ***13***

Formic acid (0.88 ml, 23.19 mmol) was added dropwise to acetic anhydride (1.8 ml, 18.84 mmol) at 0°C under nitrogen. An air condenser was fitted and the reaction mixture was heated to 60°C and kept at that temperature for 1 hour. A solution of **7** (1.5 g, 7.25 mmol) in tetrahydrofuran (10 ml) was then added and the colourless solution was heated at 65°C for 2.5 hours. The reaction mixture was then concentrated *in vacuo* and purified by column chromatography on silica eluting with ethyl acetate/light petroleum (10%) to afford **13** (1.60 g, 85%) as a colourless oil (found: C, 66.54; H, 7.35; N, 5.94;

$C_{13}H_{17}O_3N$ requires C, 66.35; H, 7.29; N, 5.96%); $[\alpha]_D^{22}=-82.5$ (*c* 2, $CHCl_3$); ν_{max} (film)/cm^{-1} 2966, 1743 (C=O), 1682 (HC=O), 1596, 1496; δ_H (250 MHz; $CDCl_3$) 0.91 (3H, d, *J* 6.6, $CH(CH_3)_2$), 0.99 (3H, d, *J* 6.6, $CH(CH_3)_2$), 2.36 (1H, dsept, *J* 10.1, 6.6, $CH(CH_3)_2$), 3.54 (3H, s, CO_2CH_3), 4.64 (1H, d, *J* 10.1, $CHCO_2Me$), 7.24–7.43 (5H, m, Ar), 6.35 (1H, s, CHO); δ_C (63 MHz; $CDCl_3$) 19.8 ($CH(CH_3)_2$), 20.3 ($CH(CH_3)_2$), 27.8 ($CH(CH_3)_2$), 52.1 (CO_2CH_3), 63.8 ($CHCH(CH_3)_2$), 126.4 (Ar), 127.7 (Ar), 129.5 (Ar), 39.7 (Ar), 163.2 (HC=O), 170.9 (C=O); *m/z* (EI) 235 (M^+, 13%), 206 (100), 120 (12), 115 (26), 77 (14). (Found: M^+, 235.1210. $C_{13}H_{17}NO_3$ requires *M*, 235.1208.)

6.10. (S)-N-*Methyl*-N-*phenyl-2-amino-3-methylbutan-1-ol* ***14***

A solution of **13** (1.29 g, 5.5mmol) in tetrahydrofuran (20 ml) was added to a suspension of lithium aluminium hydride (1.05 g, 27.5 mmol) in diethyl ether (20 ml) at 0°C under nitrogen. The suspension was stirred for a further 15 minutes and then quenched at 0°C by careful addition of water (1 ml), aqueous sodium hydroxide (15% w/v, 1 ml) and water (3 ml). The resulting white suspension was filtered through a pad of Celite® and the residue washed with tetrahydrofuran (25 ml). The organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to yield a white solid which was recrystallised to afford **14** (1.04 g, 98%) as a white solid, mp 78–79°C (light petroleum) (found: C, 74.42; H, 9.94; N, 7.11; $C_{12}H_{19}ON$ requires C, 74.55; H, 9.91; N, 7.25%); $[\alpha]_D^{22}=-153.8$ (*c* 1.3, $CHCl_3$); ν_{max} (film)/cm^{-1} 3323 (OH), 2960, 2896, 2802, 1600, 1570; δ_H (250 MHz; $CDCl_3$) 0.76 (3H, d, *J* 6.7, $CH(CH_3)_2$), 0.93 (3H, d, *J* 6.7, $CH(CH_3)_2$), 1.75–1.97 (1H, m, $CH(CH_3)_2$), 2.05 (1H, brs, CH_2OH), 2.78 (3H, s, NCH_3), 3.52–3.19 (2H, m, CH_2OH), 3.76–3.91 (1H, br m, $CHCH(CH_3)_2$), 6.71–7.32 (5H, m, Ar); δ_C (63 MHz; $CDCl_3$) 20.0 ($CH(CH_3)_2$), 20.89 ($CH(CH_3)_2$), 29.04 ($CH(CH_3)_2$), 30.1 (NCH_3), 61.0 (CH_2OH), 67.7 ($CHCH(CH_3)_2$), 113.7 (Ar), 117.4 (Ar), 129.2 (Ar), 152.2; *m/z* (EI) 193 (M^+, 20%), 162 (100), 150 (45). (Found: M^+, 193.1463. $C_{12}H_{19}NO$ requires *M*, 193.1466.)

6.11. (S)-N-*Methyl*-N-*phenyl-2-amino-3-methyl-1-thiolacetyl butane*

Identical to the preparation of **12**, gave the *N*-methyl,*N*-phenyl thioacetate (83%) as a colourless oil (found: C, 67.06; H, 8.59; N, 5.52; S, 12.66; $C_{14}H_{21}ONS$ requires C, 66.89; H, 8.42; N, 5.52; S, 12.75%); $[\alpha]_D^{22}=+9.0$ (*c* 1.2, $CHCl_3$); ν_{max} (film)/cm^{-1} 2924, 1689 (C=O), 1598, 1504; δ_H (250 MHz; $CDCl_3$) 0.82 (3H, d, *J* 6.6, $CH(CH_3)_2$), 1.07 (3H, d, *J* 6.6, $CH(CH_3)_2$), 1.81–2.02 (1H, m, $CH(CH_3)_2$), 2.22 (3H, s, $SCOCH_3$), 2.71 (3H, s, NCH_3), 2.98 (1H, dd, *J* 13.7, 11.0, $CHCH\alpha H\beta$), 3.49 (1H, dd, *J* 13.7, 3.7, $CHCH\alpha H\beta$), 3.64 (1H, ddd, *J* 11.0, 9.7, 3.7, $CHCH(CH_3)_2$), 6.62–7.25 (5H, m, Ar); δ_C (63 MHz; $CDCl_3$) 20.4 ($CH(CH_3)_2$), 20.7 ($CH(CH_3)_2$), 30.6 ($CH(CH_3)_2$), 31.3 (CH_2S), 32.0 ($CHCH(CH_3)_2$), 30.1 ($SCOCH_3$), 63.5 (NCH_3), 112.5 (Ar), 116.3 (Ar), 129.0 (Ar), 152.2 (C=O); *m/z* (EI) 251 (M^+, 32%), 208 (69), 166 (32), 162 (100), 77 (34). (Found: M^+, 251.1351. $C_{14}H_{21}NOS$ requires *M*, 251.1344.)

6.12. (S)-N-*Methyl*-N-*phenyl-2-amino-3-methylbutan-1-thiol* ***2***

Identical to the preparation of **1**, gave **2** (98%) as a colourless oil; $[\alpha]_D^{22}=-93.8$ (*c* 0.8, $CHCl_3$); ν_{max} (film)/cm^{-1} 2959, 2566w (SH), 1598, 1504; δ_H (250 MHz; $CDCl_3$) 0.73 (3H, d, *J* 6.6, $CH(CH_3)_2$), 0.92 (3H, d, *J* 6.6, $CH(CH_3)_2$), 1.38 (1H, dd, *J* 8.6, 5.5, SH), 1.8 (1H, dsept, *J* 9.5, 6.6, $CH(CH_3)_2$), 2.67 (3H, s, NCH_3), 2.68–2.80 (2H, m, CH_2SH), 3.52 (1H, dt, *J* 9.5, 4.9, $CHCH(CH_3)_2$), 6.57–7.19 (5H, m, Ar); δ_C (63 MHz; $CDCl_3$) 20.5 ($CH(CH_3)_2$), 20.9 ($CH(CH_3)_2$), 26.3 (CH_2SH), 30.2 ($CH(CH_3)_2$), 31.8 (NCH_3), 67.3 ($CHCH(CH_3)_2$), 112.7 (Ar), 116.5 (Ar), 129.3 (Ar), 151.1; *m/z* (CI) 209 (M^+, 33%), 166 (64), 162 (100), 132 (16), 107 (12), 86 (10). (Found: M^+, 209.1244. $C_{12}H_{19}NS$ requires *M*, 209.1238.)

*6.13. (*S*)-*N*-Phenyl-2-amino-3-methylbutan-1-ol **15***

Identical to the preparation of **9**, gave **15** (93%) as a colourless oil (found: C, 73.72; H, 9.41; N, 7.82; $C_{17}H_{21}ON$ requires C, 73.70; H, 9.56; N, 7.81%); $[\alpha]_D^{22}=-163$ (*c* 1, $CHCl_3$); ν_{max} (film)/cm^{-1} 3396 (OH), 3052, 3021, 2959, 1505; δ_H (250 MHz; $CDCl_3$) 0.92 (3H, d, *J* 6.7, $CH(CH_3)_2$), 1.00 (3H, d, *J* 6.7, $CH(CH_3)_2$), 1.79–2.01 (1H, m, $CH(CH_3)_2$), 2.81 (1H, br s, OH), 3.25–3.37 (1H, m, $CHCH(CH_3)_2$), 3.53 (1H, dd, *J* 11.0, 7.0, $CHCH\alpha H\beta$), 3.77 (1H, dd, *J* 11.0, 4.3, $CHCH\alpha H\beta$), 6.65–6.75 (5H, m, Ar); δ_C (63 MHz; $CDCl_3$) 19.1 ($CH(CH_3)_2$), 19.2 ($CH(CH_3)_2$), 30.2 ($CH(CH_3)_2$), 60.9 (CH_2OH), 62.7 ($CHCH(CH_3)_2$), 113.7 (Ar), 117.7 (Ar), 129.4 (Ar), 148.5 (Ar); *m/z* (EI) 179 (M^+, 23%), 148 (100), 136 (37), 118 (21). (Found: M^+, 179.1314. $C_{17}H_{21}NO$ requires *M*, 179.1310.)

*6.14. (*S*)-*N*-Phenyl-2-amino-3-methyl-1-thiophenylbutane **3***

A solution of **15** (2.0 g, 11.17 mmol), diphenylsulfide (7.32 g, 33.5 mmol) and tributylphosphine (9.04 g, 44.7 mmol) in tetrahydrofuran (15 ml) was heated in a sealed tube for 72 hours at 80°C. The reaction mixture was diluted with diethyl ether (25 ml) and the resulting white precipitate was filtered off and washed with diethyl ether (2×10 ml). The combined organic layers were washed with 2M sodium hydroxide (15 ml), brine (25 ml), dried ($MgSO_4$) and concentrated *in vacuo* to yield a brown oil. Purification of the residue by column chromatography on silica eluting with ethyl acetate/light petroleum (1.5%) gave **3** (2.55 g, 81%) as a colourless oil (found: C, 75.12; H, 7.91; N, 5.18; S, 11.88; $C_{17}H_{21}NS$ requires C, 75.23; H, 7.80; N, 5.16; S, 11.81%); $[\alpha]_D^{22}=+28.7$ (*c* 1.3, $CHCl_3$); ν_{max} (film)/cm^{-1} 3401 (NH), 2959, 1600, 1505, 1480, 753; δ_H (250 MHz; $CDCl_3$) 0.98 (6H, d, *J* 6.7, $CH(CH_3)_2$), 2.04–2.25 (1H, m, $CH(CH_3)_2$), 3.09 (2H, d, *J* 6.1, CH_2SPh), 3.42 (1H, q, *J* 5.5, $CHCH(CH_3)_2$), 3.66 (1H, br s, NH), 6.46–7.36 (10H, m, Ar); δ_C (63 MHz; $CDCl_3$) 17.8 ($CH(CH_3)_2$), 19.4 ($CH(CH_3)_2$), 30.5 ($CH(CH_3)_2$), 36.8 (CH_2SPh), 57.8 ($CHCH(CH_3)_2$), 113.3 (Ar), 117.3 (Ar), 118.4 (Ar), 126.3 (Ar), 129.0 (Ar), 129.3 (Ar), 130.0 (Ar), 136.4 (Ar), 147.6; *m/z* (EI) 271 (M^+, 21%), 148 (100), 118 (18). (Found: M^+, 271.1394. $C_{17}H_{21}NS$ requires *M*, 271.1395.)

*6.15. (*S*)-*N*-Phenyl-2-amino-3-methyl-1-thiolacetylbutane*

Identical to the preparation of **12**, gave the thiolacetate (83%) as a colourless oil; $[\alpha]_D^{22}=+13.3$ (*c* 3.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3397 (NH), 2960, 1686 (C=O), 1601, 1508; δ_H (250 MHz; $CDCl_3$) 0.90 (3H, d, *J* 6.4, $CH(CH_3)_2$), 0.93 (3H, d, *J* 6.4, $CH(CH_3)_2$), 1.82–2.00 (1H, m, $CH(CH_3)_2$), 2.30, (3H, s, $SCOCH_3$), 3.03 (1H, dd, *J* 13.7, 5.8, $CHCH\alpha H\beta$), 3.10 (1H, dd, *J* 13.7, 7.3, $CHCH\alpha H\beta$), 3.38 (1H, m, $CHCH(CH_3)_2$), 3.65 (1H, br s, NH), 6.55–7.18 (5H, m, Ar); δ_C (63 MHz; $CDCl_3$) 18.0 ($CH(CH_3)_2$), 18.8 ($CH(CH_3)_2$), 30.7 ($CH(CH_3)_2$), 31.3 ($SCOCH_3$), 31.5 (CH_2S), 58.5 ($CHCH(CH_3)_2$), 113.0 (Ar), 117.1 (Ar), 129.3 (Ar), 147.8 (Ar), 196.5 (C=O); *m/z* (EI) 237 (M^+, 15%), 194 (25), 152 (31), 148 (100), 118 (14), 77 (14). (Found: M^+, 237.1185. $C_{13}H_{19}NOS$ requires *M*, 237.1187.)

*6.16. (*S*)-*N*-Phenyl-2-amino-3-methylbutan-1-thiol **4***

Identical to the preparation of **1**, gave **4** (98%) as a colourless oil; $[\alpha]_D^{22}=-20.0$ (*c* 2.3, $CHCl_3$); ν_{max} (film)/cm^{-1} 3396 (NH), 2563 (SH), 1601, 1503; δ_H (250 MHz; $CDCl_3$) 0.95 (3H, d, *J* 6.9, $CH(CH_3)_2$), 0.99 (3H, d, *J* 6.9, $CH(CH_3)_2$), 1.37 (1H, dd, *J* 8.9, 7.3, SH), 1.90–2.06 (1H, m, $CH(CH_3)_2$), 2.66–2.78 (2H, m, CH_2SH), 3.23–3.35 (1H, m, $CHCH(CH_3)_2$), 3.68 (1H, br s, NH), 6.54–7.22 (5H, m, Ar); δ_C (63 MHz; $CDCl_3$) 18.4 ($CH(CH_3)_2$), 19.5 ($CH(CH_3)_2$), 26.7 (CH_2SH), 30.3 ($CH(CH_3)_2$), 60.0

(*C*HCH(CH_3)$_2$), 113.5 (Ar), 117.4 (Ar), 129.5 (Ar), 147.8 (Ar); *m/z* (EI) 195 (M^+, 18%), 152 (12), 148 (100), 118 (27), 93 (14), 77 (17). (Found: M^+, 195.1073. $C_{11}H_{17}NS$ requires *M*, 195.1082.)

6.17. (S)-N-para-*Toluenesulfonyl-2-amino-3-methyl-1-thiophenylbutane* **5**

Sodium hydride (80% in mineral oil, 37.5 mg 1.25 mmol) was washed with hexane and dried under high vacuum for 15 minutes. Thiophenol (0.13 ml, 1.25 mmol) was added to a suspension of the sodium hydride in dimethylformamide (2 ml) at 0°C and the suspension left to stir for 30 minutes at ambient temperature. A solution of **16** (248 mg, 1.04 mmol) in diethyl ether (3 ml) was added dropwise to the reaction mixture and stirring was continued for a further 30 minutes. The reaction was then quenched upon addition of aqueous sodium bicarbonate (25 ml) and the aqueous layers were extracted with dichloromethane (3×25 ml). The combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo* to yield an oily brown solid. Recrystallisation from light petroleum/ethyl acetate (9:1) gave **5** (272 mg, 75%) as a white solid, mp 78–79°C (light petroleum) (found: C, 61.69; H, 6.63; N, 4.11; S, 18.37; $C_{18}H_{23}NO_2S_2$ requires C, 61.86; H, 6.63; N, 4.01; S, 18.35%); $[\alpha]_D^{22}=-29.3$ (*c* 0.8, $CHCl_3$); ν_{max} (film)/cm^{-1} 3280, 3060, 2964, 2929, 2874, 1599, 1496; δ_H (250 MHz; $CDCl_3$) 0.76 (3H, d, *J* 6.7, CH(C*H*$_3$)$_2$), 0.82 (3H, d, *J* 6.7, CH(C*H*$_3$)$_2$), 1.98–2.11 (1H, m, C*H*(CH_3)$_2$), 2.38 (3H, s, Ar–CH_3), 2.76 (1H, dd, *J* 13.4, 6.7, C*H*αHβSPh), 3.06 (1H, dd, *J* 13.4, 4.9, CHα*H*βSPh), 3.13–3.23 (1H, m, C*H*CH(CH_3)$_2$), 7.17–7.29 (7H, m, Ar), 7.64 (2H, d, *J* 8.2, Ar); δ_C (63 MHz, $CDCl_3$), 17.1 (CH(*C*H$_3$)$_2$), 18.9 (CH(*C*H$_3$)$_2$), 21.5 (Ar*C*H_3), 29.6 (*C*H(CH_3)$_2$), 36.5 (*C*H_2SPh), 57.9 (*C*HCH(CH_3)$_2$), 126.5 (Ar), 127.1 (Ar), 129.0 (Ar), 129.6 (Ar), 129.8 (Ar), 135.4 (Ar), 137.6 (Ar), 143.3 (Ar); *m/z* (EI) 349 (M^+, 14%), 226 (100), 155 (74), 124 (24), 91 (77), 84 (19). (Found: M^+, 349.1181. $C_{18}H_{23}NO_2S_2$ requires *M*, 349.1170.)

6.18. (S)-N-para-*Toluenesulfonyl-2-amino-3-methylbutane-1-thiol* **6**

Using Ph_3SiSH: Triphenylsilylthiol (550 mg, 1.88 mmol) followed by triethylamine (174 mg, 1.72 mmol) were added to a 0.4M methanol solution of **16**. After stirring at ambient temperature for 15 hours the reaction mixture was poured into water (50 ml) and extracted with dichloromethane (3×25 ml). The combined organic layers were concentrated *in vacuo* to give the crude product as a yellow oil. Purification was by column chromatography, eluting with ethyl acetate/light petroleum (25%) yielding **6** (280 mg, 66%) as a colourless oil; $[\alpha]_D^{22}=-15.2$ (*c* 2.3, $CHCl_3$); ν_{max} (film)/cm^{-1} 3295 (NH), 2957, 2876, 1328, 1099; δ_H (250 MHz; $CDCl_3$) 0.80 (6H, t, *J* 6.7, CH(C*H*$_3$)$_2$), 1.59 (1H, br s, S*H*), 1.87 (1H, br s, C*H*(CH_3)$_2$), 2.42 (3H, s, Ar–CH_3), 2.46 (1H, m, C*H*αHβSH), 2.65 (1H, m, CHα*H*βSH), 3.11 (1H, m, C*H*CHCH_3), 4.75 (1H, d, *J* 8.2, N*H*), 7.26–7.78 (4H, m, Ar); δ_C (63 MHz; $CDCl_3$), 18.4 (CH(*C*H$_3$)$_2$), 19.2 (CH(*C*H$_3$)$_2$), 22.0 (Ar*C*H_3), 26.8 (*C*H_2SH), 28.1 (*C*H(CH_3)$_2$), 57.9 (*C*HCH(CH_3)$_2$), 127.1 (Ar), 129.0 (Ar), 137.6 (Ar), 143.3 (Ar); *m/z* (CI) 274 (MH^+, 24%), 226 (100), 155 (13), 148 (20), 91 (28). (Found: M^+, 274.0924. $C_{12}H_{20}NO_2S_2$ requires *M*, 274.0935.)

Via Mitsunobu/reduction procedure: Identical to the preparation of **12**, gave the *N-para*-toluenesulfonyl thiolacetate (72%) as a white solid; mp 99–101°C (diethyl ether) (found: C, 53.41; H, 6.44; N, 4.35; S, 20.33; $C_{14}H_{21}NS_2O_3$ requires C, 53.31; H, 6.71; N, 4.44; S, 20.33%); $[\alpha]_D^{22}=-9.1$ (*c* 1.0, CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3308s, 2966s, 1666s (C=O), 1326s, 1162s; δ_H (250 MHz; $CDCl_3$) 0.85 (3H, d, *J* 6.7, CH(C*H*$_3$)$_2$), 0.87 (3H, d, *J* 6.7, CH(C*H*$_3$)$_2$), 1.78–1.93 (1H, m, C*H*(CH_3)$_2$), 2.19 (3H, s, SCOC*H*$_3$), 2.42 (3H, s, ArC*H*$_3$), 2.81 (1H, dd, *J* 14.3, 5.2, CHC*H*αHβ), 2.92 (1H, dd, *J* 14.3, 7.6, CHCHα*H*β), 3.26 (1H, tt, *J* 8.0, 5.1, C*H*CH(CH_3)$_2$), 4.68 (1H, d, *J* 8.2, N*H*), 7.24–7.32 (2H, m, Ar), 7.68–7.76 (2H, m, Ar); δ_C (63 MHz; $CDCl_3$) 17.9 (CH(*C*H$_3$)$_2$), 18.3 (CH(*C*H$_3$)$_2$), 21.5 (Ar*C*H_3), 30.4

(*C*H(CH$_3$)$_2$), 31.0 (*C*H$_2$S), 31.8 (SCO*C*H$_3$), 59.4 (*C*HCH(CH$_3$)$_2$), 127.2 (Ar), 129.5 (Ar), 138.2 (Ar), 143.1 (Ar), 196.1 (C=O); *m/z* (EI) 315 (M$^+$, 9%), 272 (33), 226 (100), 155 (31), 139 (10%), 91 (34%). (Found: M$^+$, 315.0972. $C_{14}H_{21}NO_3S_2$ requires *M*, 315.0963.)

Treatment of the the *N-para*-toluenesulfonyl thiolacetate (176 mg, 0.6 mmol) from above with lithium aluminium hydride (85 mg, 2.3 mmol) under exactly the same conditions as for the preparation of **1** gave **6** as a white solid (145 mg, 95%) with physical data identical to that prepared above.

*6.19. (*R*)*-N-para-*Toluenesulfonyl-2-amino-2-phenyl-1-thiophenylethane* ***18***

A solution of **21** (1.95 g, 6.7 mmol), diphenyldisulfide (4.39 g, 20.1 mmol) and tributylphosphine (6.68 ml, 26.8 mmol) in tetrahydrofuran (20 ml) was heated at 80°C in a sealed tube for 72 hours. The reaction mixture was diluted with diethyl ether (50 ml), washed with 2M sodium hydroxide (20 ml) and brine (30 ml) and concentrated *in vacuo* to afford a brown oil which was purified by column chromatography on silica eluting with ethyl acetate/light petroleum (20%) to afford an oily white solid. Recrystallisation from light petroleum gave **18** (578 mg, 65%) as a white crystalline solid, mp 98–99°C (found: C, 65.08; H, 5.59; N, 3.59; S, 16.77; $C_{21}H_{21}NO_2S_2$ requires C, 65.22; H, 5.52; N, 3.65; S, 16.72%); $[\alpha]_D^{22}$=+18.9 (*c* 1.8, $CHCl_3$); ν_{max} (film)/cm^{-1} 3274 (NH), 1328, 1157; δ_H (250 MHz; $CDCl_3$) 2.38 (3H, s, ArC*H*$_3$), 3.20 (2H, d, *J* 6.7, C*H*$_2$S), 4.27 (1H, m, C*H*Ph), 5.32 (1H, d, *J*.4.9, N*H*), 7.05–7.31 (12H, m, Ar), 7.48 (2H, d, J 8.1, Ar); δ_C (63 MHz; $CDCl_3$) 25.2 (*C*H$_2$SPh), 35.3 (Ph*C*H$_3$), 59.6 (Ar*C*H), 126.6 (Ar), 127.0 (Ar), 127.3 (Ar), 127.9 (Ar), 128.2 (Ar), 128.6 (Ar), 129.0 (Ar), 129.5 (Ar), 136.2 (Ar), 137.0 (Ar), 137.6 (Ar), 142.4 (Ar); *m/z* (EI) 383 (M$^+$, 5%), 260 (100), 199 (22), 155 (45), 124 (15), 91 (62). (Found: M$^+$, 383.1013. $C_{21}H_{21}NO_2S_2$ requires *M*, 383.1014.)

*6.20. (*S*)*-N,N-*Dibenzyl-2-amino-3-methyl-1-butanol* ***24***

Benzyl bromide (1.41 ml, 11.85 mmol) was added dropwise to a well-stirred suspension of L-valinol (555 mg, 5.39 mmol) and anhydrous potassium carbonate (1.86 g, 13.47 mmol) in ethanol (30 ml) at room temperature. The reaction mixture was stirred for 24 hours, filtered through a pad of Celite™, washed with ethyl acetate (50 ml) and concentrated *in vacuo*. The resultant brown oil was re-dissolved in ethyl acetate (30 ml), washed with water (2×25 ml), aqueous sodium bicarbonate (25 ml), brine (25 ml), dried ($MgSO_4$) and concentrated to yield a colourless oil. Purification by column chromatography on silica eluting with ethyl acetate/light petroleum (15%) gave **24** (1.39 g, 91%) as a colourless oil; $[\alpha]_D^{22}$=+24.4 (*c* 0.8, $CHCl_3$) (lit.,[40] $[\alpha]_D^{22}$=+23.5); ν_{max} (film)/cm^{-1} 3418 (OH); δ_H (250 MHz; $CDCl_3$) 0.89 (3H, d, *J* 6.7, CH(C*H*$_3$)$_2$), 0.93 (3H, d, *J* 6.7, CH(C*H*$_3$)$_2$), 1.95–2.15 (1H, m, C*H*(CH$_3$)$_2$), 2.54 (1H, ddd, *J* 9.8, 7.9, 4.6, C*H*CH(CH$_3$)$_2$), 3.43 (1H, t, *J* 9.8, CHC*H*αHβ), 3.57 (1H, dd, *J* 10.7, 4.6, CHCHα*H*β), 3.67 (2H, d, *J* 13.1, ArC*H*$_2$), 3.89 (2H, d, *J* 13.3, ArC*H*$_2$), 7.15–7.43 (10H, m, Ar); δ_C (63 MHz; $CDCl_3$) 20.1 (CH(*C*H$_3$)$_2$), 22.8 (CH(*C*H$_3$)$_2$), 27.6 (*C*H(CH$_3$)$_2$), 54.2 (Ar*C*H$_2$), 59.2 (*C*HCH(CH$_3$)$_2$), 64.9 (CH$_2$OH), 127.2 (Ar), 128.5 (Ar), 129.2 (Ar), 139.7 (Ar.)

*6.21. (*S*)*-N,N-*Dibenzyl-2-amino-3-methyl-1-thiolacetylbutane*

Identical to the preparation of **12**, gave the *N,N*-dibenzyl thioacetate (83%) as a colourless oil (found: C, 73.48; H, 8.13; N, 4.02; S, 9.54; $C_{21}H_{27}NOS$ requires C, 73.86; H, 7.97; N, 4.1; S, 9.39%); $[\alpha]_D^{22}$=−87.0 (*c* 1, $CHCl_3$); ν_{max} (film)/cm^{-1} 2958, 1689 (C=O); δ_H (250 MHz; $CDCl_3$) 0.90 (3H, d, *J* 6.7, CH(C*H*$_3$)$_2$), 1.02 (3H, d, *J* 6.7, CH(C*H*$_3$)$_2$), 1.99 (1H, sept, *J* 6.7, C*H*(CH$_3$)$_2$), 2.34 (3H, s, SCOC*H*$_3$), 2.40–2.54 (1H, m, C*H*CH(CH$_3$)$_2$), 3.05 (1H, dd, *J* 13.9, 5.4, C*H*αCHβS), 3.28 (1H, dd, *J*

13.9, 6.6, CHαC*H*βS), 3.62 (2H, d, *J* 13.6, C*H*$_2$Ar), 3.62 (2H, d, *J* 13.6, C*H*$_2$Ar), 7.17–7.45 (10H, m, Ar); δ_C (63 MHz; $CDCl_3$) 20.3 (CH(*C*H$_3$)$_2$), 21.3 (CH(*C*H$_3$)$_2$), 27.1 (S*C*H$_2$), 29.7 (*C*H(CH$_3$)$_2$), 30.6 (SCO*C*H$_3$), 54.2 (N*C*H$_2$), 62.9 (*C*HCH(CH$_3$)$_2$), 126.9 (Ar), 128.1 (Ar), 129.0 (Ar), 139.9 (Ar), 195.8 (C=O); *m/z* (EI) 341 (M^+, 14%), 298 (90), 252 (91), 91 (100). (Found: M^+, 341.1805. $C_{21}H_{27}NOS$ requires *M*, 341.1813.)

6.22. (S)-N,N-*Dibenzyl-2-amino-3-methylbutan-1-thiol* **22**

Identical to the preparation of **1**, gave **22** (98%) as a colourless oil; $[\alpha]_D^{22}=-45.7$ (*c* 1.1, $CHCl_3$); ν_{max} (film)/cm^{-1} 2957, 2569w (SH), 1453; δ_H (250 MHz; $CDCl_3$) 0.85 (3H, d, *J* 6.7, CH(C*H*$_3$)$_2$), 0.94 (3H, d, *J* 6.7, CH(C*H*$_3$)$_2$), 1.58 (1H, dd, *J* 8.2, 6.1, S*H*), 1.95–2.11 (1H, m, C*H*(CH$_3$)$_2$), 2.37–2.48 (1H, m, C*H*CH(CH$_3$)$_2$), 2.50–2.63 (1H, m, CHC*H*αHβ), 2.70–2.83 (1H, m, CHCHα*H*β), 3.48–3.67 (4H, m, ArC*H*$_2$), 7.10–7.39 (10H, m, Ar); δ_C (63 MHz; $CDCl_3$) 20.3 (CH(*C*H$_3$)$_2$), 21.5 (CH(*C*H$_3$)$_2$), 22.2 (S*C*H$_2$), 28.8 (*C*H(CH$_3$)$_2$), 54.4 (Ar*C*H$_2$), 65.4 (*C*HCH(CH$_3$)$_2$), 126.9 (Ar), 128.2 (Ar), 129.1 (Ar), 139.9 (Ar); *m/z* (CI) 300 (MH^+, 6%), 256 (44), 252 (100), 210 (16), 91 (89). (Found: M^+, 300.1796. $C_{19}H_{26}NS$ requires *M*, 300.1786.)

6.23. (S)-*3-Methyl-2-piperidinylbutan-1-ol* **25**

1,5-Dibromopentane (14.1 ml, 0.1 mol) was added dropwise to a suspension of L-valinol (5.4 g, 0.051 mol) and potassium carbonate (35.5 g, 0.26 mol) in ethanol (100 ml).The reaction mixture was heated to reflux for 48 hours. The solids were filtered off and washed with ethanol (25 ml). Evaporation of the solvents *in vacuo* afforded a pale yellow oil. Purification by flash column chromatography on silica eluting with ethyl acetate/light petroleum (20%) afforded **25** (6.94g, 78%) as a viscous pale yellow oil (found: C, 70.14; H, 12.44; N, 8.26; $C_{10}H_{21}NO$ requires C, 70.12; H, 12.36; N, 8.18%); $[\alpha]_D^{22}=-43.5$ (*c* 1.2, $CHCl_3$); ν_{max} (film)/cm^{-1} 3424 (OH), 2932, 1471, 1451; δ_H (250 MHz; $CDCl_3$) 0.76 (3H, d, *J* 6.7, CH(C*H*$_3$)$_2$), 0.98 (3H, d, *J* 6.7, CH(C*H*$_3$)$_2$), 1.37–1.62 (6H, m, –CH$_2$–), 1.8 (1H, dsept, *J* 8.5, 6.7, C*H*(CH$_3$)$_2$), 2.24 (1H, ddd, *J* 10.1, 8.5, 5.3, C*H*CH(CH$_3$)$_2$), 2.43–2.57 (2H, m, NCH$_2$–), 2.73–2.86 (2H, m, NCH$_2$–), 3.12 (1H, t, *J* 10.1, C*H*αHβOH), 3.46 (1H, dd, *J* 10.1, 5.3, C*H*αHβOH); δ_C (63 MHz; $CDCl_3$); 19.8 (CH(*C*H$_3$)$_2$), 22.8 (CH(*C*H$_3$)$_2$), 24.5 (–*C*H$_2$–), 27.2 (–*C*H$_2$–), 28.0 (*C*H(CH$_3$)$_2$), 50.0 (–*C*H$_2$N–), 58.7 (*C*H$_2$OH), 71.5 (*C*HCH(CH$_3$)$_2$); *m/z* (EI) 171 (M^+, 63%), 154 (100), 84 (23). (Found: M^+, 171.1624. $C_{10}H_{21}NO$ requires *M*, 171.1623.)

6.24. (S)-*3-Methyl-2-piperidinyl-1-thiolacetylbutane*

Identical to the preparation of **12**, gave the piperidinyl thioacetate (84%) as a mobile colourless oil (found: C, 62.84; H, 10.28; N, 6.01; S, 14.04; $C_{12}H_{23}NOS$ requires C, 62.84; H, 10.11; N, 6.11; S, 13.98%); $[\alpha]_D^{22}=+31.9$ (*c* 1.4, $CHCl_3$); ν_{max} (film)/cm^{-1} 2932, 1692 (C=O), 1130, 1099; δ_H (250 MHz; $CDCl_3$) 0.84 (3H, d, *J* 6.7, CH(C*H*$_3$)$_2$), 0.93 (3H, d, *J* 6.7, CH(C*H*$_3$)$_2$), 1.27–1.50 (6H, m, –C*H*$_2$–), 1.75 (1H, sept, *J* 6.72, C*H*(CH$_3$)$_2$), 2.15–2.24 (1H, m, C*H*CH(CH$_3$)$_2$), 2.25 (3H, s, SCOC*H*$_3$), 2.35–2.45 (2H, m, –C*H*$_2$N), 2.47–2.57 (2H, m, –C*H*$_2$N), 2.9 (2H, d, *J* 5.8, C*H*$_2$SCO); δ_C (63 MHz; $CDCl_3$) 20.4 (CH(*C*H$_3$)$_2$), 21.2 (CH(*C*H$_3$)$_2$), 25.0 (–CH$_2$–), 26.7 (–CH$_2$–), 28.8 (*C*H$_2$SCO), 30.0 (*C*H(CH$_3$)$_2$), 30.5 (CO*C*H$_3$), 50.5 (–CH$_2$N), 70.4 (*C*HCH(CH$_3$)$_2$), 196.3 (*C*=O); *m/z* (EI) 229 (M^+, 11%), 188 (16%), 186 (100), 144 (58). (Found: M^+, 229.1500. $C_{12}H_{23}NOS$ requires *M*, 229.1500.)

6.25. (S)-3-Methyl-2-piperidinylbutan-1-thiol **23**

Identical to the preparation of **1** except the organic layer from the Celite™ plug was passed through a 2 cm pad of silica which was then washed with ethyl acetate/light petroleum (20%, 25 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford **23** (79 mg, 82%) as a pungent colourless oil; $[\alpha]_D^{22}$=+31.7 (*c* 1.2, $CHCl_3$); ν_{max} (film)/cm^{-1} 2932, 2852, 2730, 2524 (SH), 1097; δ_H (250 MHz; $CDCl_3$) 0.82 (3H, d, *J* 6.72, $CH(CH_3)_2$), 0.89 (3H, d, *J* 6.7, $CH(CH_3)_2$), 1.28–1.57 (6H, m, $-CH_2-$), 1.85 (1H, sept, *J* 6.7, $CH(CH_3)_2$), 2.19–2.25 (1H, m, $CHCH(CH_3)_2$), 2.48–2.64 (6H, m, 2×CH_2N and CH_2SH); δ_C (63 MHz; $CDCl_3$) 20.2 ($CH(CH_3)_2$), 22.0 ($CH(CH_3)_2$), 23.6 ($-CH_2-$), 25.0 ($-CH_2-$), 26.8 (CH_2SH), 29.2 ($CH(CH_3)_2$), 50.4 ($-CH_2N$), 72.9 ($CHCH(CH_3)_2$); *m/z* (EI) 187 (M^+, 3%), 144 (79), 140 (100), 111 (21), 84 (22). (Found: M^+, 187.1396. $C_{10}H_{21}NS$ requires *M*, 187.1395.)

6.26. Addition of diethylzinc to aldehydes

Diethylzinc (1M in hexanes: 7.3 ml, 7.3 mmol) was added to a solution of ligand (0.37 mmol) and aldehyde (3.65 mmol) in toluene (20 ml) at 0°C over 10 minutes. The homogeneous yellow solutions were stirred at ambient temperature for *x* hours and then quenched by addition of 1M aqueous hydrochloric acid (5 ml). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×10 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford a colourless oil. Purification by flash column chromatography on silica eluting with ethyl acetate/light petroleum gave the desired products.

6.26.1. (R)-1-Phenylpropan-1-ol

Colourless oil, $[\alpha]_D^{22}$=+38.0 (*c* 1.2, $CHCl_3$) (82% ee by chiral GC); ν_{max} (film)/cm^{-1} 3370 (OH); δ_H (250 MHz; $CDCl_3$) 0.94 (3H, t, *J* 7.2 CH_3), 1.63–1.92 (2H, m, CH_2), 2.48 (1H, s, OH), 4.55 (1H, t, *J* 6.6, CH), 7.19–7.51 (4H, m, Ar); δ_C (63 MHz; $CDCl_3$) 10.1, 31.9, 76.0, 126.0, 127.5, 128.4.

6.26.2. (R)-1-ortho-Methoxyphenylpropan-1-ol

$[\alpha]_D^{22}$=+36.0 (*c* 2.5, PhMe) (79% ee by chiral GC); ν_{max} (film)/cm^{-1} 3386 (OH); δ_H (250 MHz; $CDCl_3$) 0.96 (3H, t, *J* 7.5 CH_3), 1.82 (2H, quin, *J* 7.5, CH_2), 2.61 (1H, s, OH), 3.82 (3H, s, OCH_3), 4.78 (1H, t, *J* 6.9, CH), 6.84–7.34 (4H, m, Ar); δ_C (63 MHz; $CDCl_3$) 10.5, 30.2, 55.3, 72.5, 110.5, 120.7, 127.1, 128.2, 132.4, 156.6.

6.26.3. (R)-1-para-Methoxyphenylpropan-1-ol

$[\alpha]_D^{22}$=+26.4 (*c* 3.3, C_6H_6) (78% ee by chiral GC); ν_{max} (film)/cm^{-1} 3382 (OH); δ_H (250 MHz; $CDCl_3$) 0.95 (3H, t, *J* 7.8 CH_3), 1.82 (2H, quin, *J* 7.8, CH_2), 2.47 (1H, br s, OH), 3.83 (3H, s, OCH_3), 4.77 (1H, t, *J* 6.8, CH), 6.84–7.32 (4H, m, Ar); δ_C (63 MHz; $CDCl_3$) 10.2, 31.8, 55.3, 75.7, 113.8, 127.2, 136.8, 159.0.

6.26.4. (R)-1-para-Tolylpropan-1-ol

$[\alpha]_D^{22}$=+34 (*c* 3.3, $CHCl_3$) (81% ee by chiral GC); ν_{max} (film)/cm^{-1} 3376 (OH); δ_H (250 MHz; $CDCl_3$) 0.91 (3H, t, *J* 8.1 CH_3), 1.62–1.92 (2H, m, CH_2), 2.03 (1H, s, OH), 2.85 (3H, s, OCH_3), 4.03 (1H, t, *J* 6.3, CH), 7.10–7.27 (4H, m, Ar); δ_C (63 MHz; $CDCl_3$) 10.2, 21.1, 31.8, 75.9, 126.0, 129.1, 137.1, 141.7.

*6.26.5. (*R*)-1-*para*-Chlorophenylpropan-1-ol*

$[\alpha]_D^{22}$=+34 (*c* 3.3, C_6H_6) (81% ee by chiral GC); ν_{max} (film)/cm^{-1} 3357 (OH); δ_H (250 MHz; $CDCl_3$) 0.87 (3H, t, *J* 7.7 CH_3), 1.57–1.87 (2H, m, CH_2), 2.03 (1H, s, O*H*), 4.04 (1H, t, *J* 6.9, C*H*), 7.17–7.34 (4H, m, Ar); δ_C (63 MHz; $CDCl_3$) 10.0, 32.0, 75.3, 127.3, 128.5.

*6.27. Methyl-(*S*)-[*N-para-*tolylsulfonyl-2-amino-3-methyl]butanoate* ***28***

Iodomethane (5.7 ml, 91.6 mmol) was added to a solution of *N*-tosyl-L-valine[15] (2.50 g, 9.16 mmol) and silver oxide (2.18 g, 9.4 mmol) in dimethylformamide (20 ml) and the dark brown reaction mixture left to stir for 12 hours at ambient temperature. The reaction was then filtered through Celite® and washed with dichloromethane (30 ml). The organic layer was washed with water (30 ml), brine (30 ml), dried ($MgSO_4$) and concentrated *in vacuo* to yield a crude yellow oil. Purification of the residue by column chromatography on silica eluting with ethyl acetate/light petroleum (15%) gave **28** (1.16 g, 74%) as a white solid, mp 62–63°C (light petroleum) (found: C, 56.16; H, 7.23; N, 4.70; S, 10.96; $C_{14}H_{21}NO_4S$ requires C, 53.12; H, 6.32; N, 5.16%); $[\alpha]_D^{22}$=−50.5 (*c* 1.9, $CHCl_3$); ν_{max} (film)/cm^{-1} 2966, 1740 (C=O), 1341, 1149; δ_H (250 MHz; $CDCl_3$) 0.91 (3H, d, *J* 6.7, CH(CH_3)$_2$), 0.98 (3H, d, *J* 6.7, CH(CH_3)$_2$), 1.96–2.15 (1H, m, C*H*(CH_3)$_2$), 2.41 (3H, s, ArCH_3), 2.86 (3H, s, CO_2CH_3), 3.41 (3H, s, NCH_3), 4.10 (1H, d, *J* 10.7, C*H*CH(CH_3)$_2$), 7.23–7.29 (2H, m, Ar), 7.62–7.69 (2H, m, Ar); δ_C (63 MHz; $CDCl_3$) 19.1 (CH(*C*H_3)$_2$), 19.2 (CH(*C*H_3)$_2$), 21.5 (Ar*C*H_3), 27.8 (*C*H(CH_3)$_2$), 30.0 (N*C*H_3), 51.3 (CO_2CH$_3$), 64.6 (*C*HCH(CH_3)$_2$), 127.4 (Ar), 129.3 (Ar), 135.9 (Ar), 143.2 (Ar), 170.7 (C=O); *m/z* (CI) 300 (M^+, 50%), 256 (25), 240 (100), 155 (30), 91 (14). (Found: MH^+, 300.1274. $C_{14}H_{22}NO_4S$ requires *M*, 300.1270.)

*6.28. (*S*)-*N*-*Methyl*-N-para-*tolylsulfonyl-2-amino-3-methylbutan-1-ol* ***29***

A solution of **28** in tetrahydrofuran (15 ml) was added dropwise to a suspension of lithium aluminium hydride (454 mg, 11.96 mmol) in tetrahydrofuran (10 ml) at 0°C. After stirring for 15 minutes the reaction was then quenched by the careful addition of water (0.5 ml), aqueous sodium hydroxide (15% w/v, 0.5 ml) and water (1.5 ml). The resulting white suspension was filtered through Celite® and the residue was washed with diethyl ether (20 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford an oily solid which was recrystallised from light petroleum to afford **29** (1.02 g, 94%) as a white solid, mp 146–147°C (ethyl acetate/light petroleum) (found: C, 57.17; H, 7.71; N, 5.08; S, 12.24; $C_{13}H_{21}NO_3S$ requires C, 57.54; H, 7.80; N, 5.16; S, 11.81%); $[\alpha]_D^{22}$=−18.2 (*c* 0.6, $CHCl_3$); ν_{max} (film)/cm^{-1} 3518 (OH), 2962, 1327, 1149; δ_H (250 MHz; $CDCl_3$) 0.72 (3H, d, *J* 6.7, CH(CH_3)$_2$), 0.89 (3H, d, *J* 6.7, CH(CH_3)$_2$), 1.69 (1H, br s, C*H*(CH_3)$_2$), 2.23 (3H, s, NCH_3), 2.39 (3H, s, ArCH_3), 3.55 (3H, br s, CH_2OH and C*H*CH(CH_3)$_2$), 7.24 (2H, d, *J* 7.5, Ar), 7.69 (2H, d, 7.5, Ar); δ_C (63 MHz; $CDCl_3$) 20.0 (CH(*C*H_3)$_2$), 20.5 (CH(*C*H_3)$_2$), 21.5 (Ar*C*H_3), 27.5 (*C*H(CH_3)$_2$), 28.6 (N*C*H_3), 61.1 (*C*H_2OH), 65.1 (*C*HCH(CH_3)$_2$), 118.8 (Ar), 127.3 (Ar), 129.6 (Ar), 137.2 (Ar), 143.2 (Ar); *m/z* (CI) 272 (MH^+, 14%), 240 (100), 228 (19), 155 (23), 91 (23). (Found: MH^+, 272.1316. $C_{13}H_{22}NO_3S$ requires *M*, 272.1320.)

*6.29. (*S*)-*N*-*Methyl*-N-para-*tolylsulfonyl-2-amino-3-methyl-1-thiolacetylbutane*

Identical to the preparation of **12** except for an additional stirring of the reaction mixture for 3 hours at room temperature. Purification by column chromatography on silica eluting with ethyl acetate/light petroleum (5%) gave *N*-methyl-*N*-*para*-tolylsulfonyl thioacetate (88%) as a colourless oil (found: C,

54.69; H, 7.11; N, 4.27; S, 19.52; $C_{15}H_{23}NO_3S_2$ requires C, 54.68; H, 7.04; N, 4.25; S, 19.46%); $[\alpha]_D^{22}$=+12.1 (*c* 1.3, $CHCl_3$); ν_{max} (film)/cm^{-1} 2966, 1691, 1334, 1159; δ_H (250 MHz; $CDCl_3$) 0.83 (3H, d, *J* 6.7, $CH(CH_3)_2$), 0.99 (3H, d, *J* 6.7, $CH(CH_3)_2$), 1.73 (1H, br s, $CH(CH_3)_2$), 2.19 (3H, s, $ArCH_3$), 2.40 (3H, $SCOCH_3$), 2.60 (3H, s, NCH_3), 2.83 (1H, dd, *J* 14.3, 10.1, CHαCHβS), 3.15 (1H, dd, *J* 14.3, 4.0, CHαCHβS), 3.74 (1H, dt, *J* 10.1, 4.0, $CHCH(CH_3)_2$), 7.26 (2H, d, *J* 7.5, Ar), 7.67 (2H, d, 7.5, Ar); δ_C (63 MHz; $CDCl_3$), 20.0 ($CH(CH_3)_2$), 20.6 ($CH(CH_3)_2$), 21.1 ($ArCH_3$), 28.7 ($CH(CH_3)_2$), 29.6 (CH_2SCO), 30.4 (NCH_3), 31.1 ($COCH_3$), 62.9 ($CH(CH_3)_2$), 127.5 (Ar), 129.3 (Ar), 137.4 (Ar), 142.9 (Ar–H), 195.0 (C=O); *m/z* (EI) 272 (M^+, 21%), 286 (63), 254 (100), 175 (13), 75 (23). (Found: M^+, 329.1116. $C_{15}H_{23}NO_3S_2$ requires *M*, 329.1119.)

*6.30. (*S*)*-N-*Methyl*-N-para-*tolylsulfonyl-2-amino-3-methylbutan-1-thiol* **26**

Identical to the preparation of **1** without purification gave **26** (255 mg, 88%) as a colourless oil; $[\alpha]_D^{22}$=+4.5 (*c* 1.2, $CHCl_3$); ν_{max} (film)/cm^{-1} 2963, 2576 (SH), 1332, 1159; δ_H (250 MHz; $CDCl_3$) 0.78 (3H, d, *J* 6.7, $CH(CH_3)_2$), 0.91 (3H, d, *J* 6.7, $CH(CH_3)_2$), 1.14 (1H, dd, *J* 9.2, 6.7, SH), 1.74 (1H, br s, $CH(CH_3)_2$), 2.34 (3H, s, $ArCH_3$), 2.45 (1H, m, CHαCHβS), 2.64 (3H, s, NCH_3), 2.66 (1H, m, CHαCHβS), 3.65 (1H, m, $CHCH(CH_3)_2$), 7.21 (2H, d, *J* 8.5, Ar), 7.69 (2H, d, 7.5, Ar); δ_C (63 MHz; $CDCl_3$) 20.1 ($CH(CH_3)_2$), 20.6 ($CH(CH_3)_2$), 21.6 (CH_2SH), 28.7 ($ArCH_3$), 30.4 (NCH_3), 65.9 ($CHCH(CH_3)_2$), 127.5 (Ar), 129.4 (Ar), 137.2 (Ar), 143.1 (Ar); *m/z* (CI) 288 (MH^+, 7%), 240 (100), 155 (23), 91 (26). (Found: MH^+, 288.1100. $C_{13}H_{21}NO_2S_2$ requires *M*, 288.1092.)

*6.31. Methyl-(*S*)-[*N-*isopropyl-2-amino-3-methyl]butanoate* **30**

A solution of L-valine methyl ester (2.2 g, 16.8 mmol) in acetone (2.43 ml, 33.6 mmol) was added to a suspension of sodium cyanoborohydride (1.046 g, 16.8 mmol) in methanol (25 ml) at room temperature. The reaction mixture was stirred for 12 hours then quenched by careful addition of water (20 ml) and aqueous KOH (10%, 20 ml). The aqueous layer was extracted with dichloromethane (3×20 ml), the combined organic layers dried ($MgSO_4$) and concentrated to afford a colourless oil. Purification of the residue by flash column chromatography on silica eluting with ethyl acetate/light petroleum (7%) gave **30** (2.43 g, 84%) as a colourless oil (found: C, 62.40; H, 11.21; N, 8.11; $C_9H_{19}NO_2$ requires C, 62.39; H, 11.05; N, 8.08%); $[\alpha]_D^{22}$=−5.8 (*c* 1.2, $CHCl_3$); ν_{max} (film)/cm^{-1} 2964, 1737 (C=O); δ_H (250 MHz; $CDCl_3$) 0.90 (3H, d, *J* 3.21, $CH(CH_3)_2$), 0.93 (3H, d, *J* 3.21, $CH(CH_3)_2$), 0.97 (3H, d, *J* 6.6, $CH(CH_3)_2$), 1.03 (3H, d, *J* 6.6, $CH(CH_3)_2$), 1.75–1.94 (1H, m, $CH(CH_3)_2$), 2.55–2.71 (1H, m, $CH(CH_3)_2$), 3.06 (1H, d, *J* 5.8, $CHCH(CH_3)_2$), 3.70 (3H, s, OCH_3); δ_C (63 MHz; $CDCl_3$) 18.8 ($CH(CH_3)_2$), 19.1 ($CH(CH_3)_2$), 22.1 ($CH(CH_3)_2$), 23.9 ($CH(CH_3)_2$), 31.8 ($CH(CH_3)_2$), 47.4 ($NCH(CH_3)_2$), 51.4 ($COOCH_3$), 64.8 ($CHCH(CH_3)_2$), 176.3 (C=O); *m/z* (EI) 173 (M^+, 2%), 130 (50), 114 (100), 88 (31), 72 (30), 55(11). (Found: M^+, 173.1418. $C_9H_{19}NO_2$ requires *M*, 173.1416.)

*6.32. (*S*)*-N-*Formyl*-N-*isopropyl-2-amino-3-methylbutan-1-ol* **31**

Identical to the preparation of **13** except the final reaction mixture was heated at 60°C for 4 hours. The reaction mixture was then concentrated *in vacuo* and filtered through a plug of silica. The residue was washed with light petroleum/ethyl acetate (20%) and the combined organic layers were concentrated *in vacuo* to give a colourless mobile oil (1.40 g, 6.96 mmol) which was used directly without any further purification.

Treatment with lithium aluminium hydride (1.06 g, 27.8 mmol) under the same conditions as for the preparation of **14**, but with purification of the residue by flash column chromatography on silica eluting with ethyl acetate/light petroleum (15%) gave **31** (1.05g, 76% over two steps) as a colourless oil (found: C, 67.82; H, 13.33; N, 8.91; $C_9H_{21}NO$ requires C, 67.82; H, 13.29; N, 8.79%); $[\alpha]_D^{22}$=+6 (*c* 1.3, $CHCl_3$); ν_{max} (film)/cm^{-1} 3408 (OH), 2963, 2873, 1468, 1383; δ_H (250 MHz; $CDCl_3$) 0.82 (3H, d, *J* 6.7, CH(CH_3)$_2$), 0.98 (3H, d, *J* 6.7, CH(CH_3)$_2$), 1.06 (3H, d, *J* 6.3, CH(CH_3)$_2$), 1.09 (3H, d, *J* 6.3, CH(CH_3)$_2$), 1.74–1.94 (1H, m, C*H*(CH$_3$)$_2$), 2.28 (3H, s, NCH_3), 2.59 (1H, ddd, *J* 10.1, 7.3, 5.2, C*H*CH(CH$_3$)$_2$), 3.17–3.04 (1H, m, NC*H*(CH$_3$)$_2$), 3.19 (1H, t, *J* 10.1, CHC*H*αHβ), 3.38 (1H, br s, CH_2O*H*), 3.45 (1H, dd, *J* 10.1, 5.2, CHC*H*αHβ), 3.38 (1H, br s, CH_2O*H*); δ_C (63 MHz; $CDCl_3$) 19.4 (CH(*C*H$_3$)$_2$), 21.4 (CH(*C*H$_3$)$_2$), 21.7 (CH(*C*H$_3$)$_2$), 22.3(CH(*C*H$_3$)$_2$), 28.0 (*C*H(CH$_3$)$_2$), 31.1 (N*C*H$_3$), 52.3 (N*C*H(CH$_3$)$_2$), 58.6 (*C*H$_2$OH), 66.1 (*C*HCH(CH$_3$)$_2$); *m/z* (CI) 160 (MH^+, 56%), 158 (100), 146 (25), 128 (31), 114 (55), 72 (22). (Found: M^+, 160.1707. $C_9H_{22}NO$ requires *M*, 160.1701.)

6.33. (S)-N-*Methyl*-N-*isopropyl-2-amino-3-methyl-1-thiolacetylbutane*

Identical to the preparation of **12** except for an additional stirring of the reaction mixture for 0.5 hours at room temperature. Purification by flash column chromatography on silica eluting with ethyl acetate/light petroleum (5%) gave the *N*-methyl-*N*-isopropyl thioacetate (77%) as a mobile colourless oil (found: C, 60.92; H, 10.81; N, 6.45; S, 14.83; $C_{11}H_{23}NOS$ requires C, 60.78; H, 10.67; N, 6.44; S, 14.75%); $[\alpha]_D^{22}$=+51 (*c* 0.7, $CHCl_3$); ν_{max} (film)/cm^{-1} 2962, 1692 (C=O), 1468, 1358, 1132; δ_H (250 MHz; $CDCl_3$) 0.89 (3H, d, *J* 7.0, CH(CH_3)$_2$), 0.92 (3H, d, *J* 7.0, CH(CH_3)$_2$), 0.99 (3H, d, *J* 6.4, CH(CH_3)$_2$), 1.02 (3H, d, *J* 6.4, CH(CH_3)$_2$), 1.68–1.88 (1H, m, C*H*(CH$_3$)$_2$), 2.22 (3H, s, SCOCH_3), 2.31 (3H, s, NCH_3), 2.45–2.57 (1H, m, C*H*CH(CH$_3$)$_2$), 2.76–2.93 (1H, m, C*H*(CH$_3$)$_2$), 3.02 (2H, d, *J* 6.1, CH_2SC); δ_C (63 MHz; $CDCl_3$), 20.1 (CH(*C*H$_3$)$_2$), 20.6 (CH(*C*H$_3$)$_2$), 20.8 (CH(*C*H$_3$)$_2$), 20.9 (CH(*C*H$_3$)$_2$), 29.3 (*C*H$_2$SCO), 30.5 (*C*H(CH$_3$)$_2$), 30.9 (*C*H(CH$_3$)$_2$), 31.5 (N*C*H$_3$), 52.5 (N*C*H(CH$_3$)$_2$), 65.2 (*C*HCH(CH$_3$)$_2$), 196.3 (C=O); *m/z* (CI) 218 (M^+, 39%), 174 (46), 128 (100), 86 (22). (Found: M^+, 218.1582. $C_{11}H_{24}NOS$ requires *M*, 218.1578.)

6.34. (S)-N-*Methyl*-N-*isopropyl-2-amino-3-methylbutan-1-thiol* ***27***

Identical to the preparation of **1** except that the reaction mixture was stirred for 30 mins at 0°C. After filtration through Celite® the organic layer was then passed through a 2 cm pad of silica which was washed with ethyl acetate/light petroleum (20%, 25 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford **27** (155 mg, 96%) as a pungent colourless oil; $[\alpha]_D^{22}$=+14.2 (*c* 0.7, $CHCl_3$); ν_{max} (film)/cm^{-1} 2962, 2874, 2537 (SH), 1466, 1382; δ_H (250 MHz; $CDCl_3$) 0.84 (3H, d, *J* 6.4, CH(CH_3)$_2$), 0.87 (3H, d, *J* 6.4, CH(CH_3)$_2$), 0.99 (3H, d, *J* 6.4, CH(CH_3)$_2$), 1.02 (3H, d, *J* 6.4, CH(CH_3)$_2$), 1.70–1.98 (1H, m, C*H*(CH$_3$)$_2$), 2.18 (3H, s, NCH_3), 2.38–2.49, (2H, m, C*H*αCHβSH and C*H*CH(CH$_3$)$_2$), 2.51–2.63 (1H, m, CHαC*H*βSH), 2.79–2.97 (1H, m, NC*H*(CH$_3$)$_2$); δ_C (63 MHz; $CDCl_3$) 20.1 (CH(*C*H$_3$)$_2$), 20.6 (CH(*C*H$_3$)$_2$), 20.8 (CH(*C*H$_3$)$_2$), 20.9 (CH(*C*H$_3$)$_2$), 29.3 (*C*H$_2$SH), 30.8 (N*C*H$_3$), 31.5 (*C*H(CH$_3$)$_2$), 52.6 (N*C*H(CH$_3$)$_2$), 65.3 (*C*HCH(CH$_3$)$_2$); *m/z* (CI) 176 (MH^+, 18%), 132 (24), 128 (100), 86 (32). (Found: M^+, 176.1468. $C_9H_{22}NS$ requires *M*, 176.1473.)

6.35. (S,S)-Bis-(N,N-*diphenyl-2-amino-3-methylbutane)-1-disulfide* ***32***

Oxygen was bubbled through a solution of **1** (20 mg, 0.07 mmol) in ethanol (4 ml) for 1 hour and the reaction mixture concentrated to dryness under reduced pressure to yield a colourless oil. Purification

by flash column chromatography on silica eluting with ethyl acetate/light petroleum (2%) afforded **32** (18 mg, 90%) as a white solid, mp 90–92°C (found: C, 75.54; H, 7.68; N, 5.19; S, 11.90; $C_{34}H_{40}N_2S_2$ requires C, 75.51; H, 7.45; N, 5.18; S, 11.86%); $[\alpha]_D^{22}$=+24.3 (*c* 0.7, $CHCl_3$); ν_{max} (film)/cm^{-1} 1588, 1495; δ_H (250 MHz; $CDCl_3$) 0.86 (6H, d, *J* 6.4, CH(C*H*$_3$)$_2$), 0.81 (6H, d, *J* 6.4, CH(C*H*$_3$)$_2$), 1.83–2.02 (2H, m, C*H*(CH$_3$)$_2$), 2.74 (2H, dd, *J* 13.3, 9.8, C*H*αCHβS), 2.88 (2H, dd, *J* 13.3, 4.0, C*H*αCHβS), 3.95 (2H, td, *J* 9.8, 4.0, C*H*CH(CH$_3$)$_2$), 6.79–7.22 (20H, m, Ar); δ_C (63 MHz; $CDCl_3$) 20.9 (CH(*C*H$_3$)$_2$), 21.3 (CH(*C*H$_3$)$_2$), 33.7 (*C*H(CH$_3$)$_2$), 40.1 (*C*H$_2$S), 65.2 (*C*HCH(CH$_3$)$_2$), 121.6 (Ar), 123.2 (Ar), 129.1 (Ar), 147.8 (Ar); *m/z* (EI) 540 (M$^+$, 2%), 224 (100), 194 (12), 104 (8), 77 (8). (Found: M$^+$, 540.2621. $C_{34}H_{40}N_2S_2$ requires *M*, 540.2633.)

*6.36. (*S,S*)-Bis-(*N-*methyl*-N-*phenyl-2-amino-3-methylbutane-1)-disulfide* ***33***

Identical to the preparation of **32**, gave **33** (84%) as a colourless oil; $[\alpha]_D^{22}$=−82.1 (*c* 1, $CHCl_3$); ν_{max} (film)/cm^{-1} 2960, 1495; δ_H (250 MHz; $CDCl_3$) 0.69 (6H, d, *J* 6.6, CH(C*H*$_3$)$_2$), 1.05 (6H, d, *J* 6.6, CH(C*H*$_3$)$_2$), 1.78–1.95 (2H, m, C*H*(CH$_3$)$_2$), 2.85 (6H, s, NC*H*$_3$), 2.58–2.70 (2H, m, C*H*CH(CH$_3$)$_2$), 2.65 (2H, dd, *J* 13.0, 5.2, CHC*H*αHβ), 3.15 (2H, dd, *J* 13.0, 6.4, CHCHα*H*β), 6.57–7.19 (10H, m, Ar); δ_C (63 MHz; $CDCl_3$) 20.6 (CH(*C*H$_3$)$_2$), 20.9 (CH(*C*H$_3$)$_2$), 26.4 (*C*H$_2$S), 30.2 (*C*H(CH$_3$)$_2$), 31.8 (*C*HCH(CH$_3$)$_2$), 67.4 (N*C*H$_3$), 112.7 (Ar), 116.5 (Ar), 129.1 (Ar), 151.6 (Ar); *m/z* (EI) 416 (M$^+$, 1%), 209 (26) 162 (100), 132 (19), 107 (17), 86 (10), 77 (15). (Found: M$^+$, 416.2321. $C_{24}H_{36}N_2S_2$ requires *M*, 416.2320.)

*6.37. (*S,S*)-Bis-(*N,N-*dibenzyl-2-amino-3-methylbutane)-1-disulfide* ***34***

Identical to the preparation of **32**, gave **34** (126 mg, 90%) as a mobile colourless oil (found: C, 76.53; H, 8.13; N, 4.81; S, 10.55; $C_{38}H_{48}N_2S_2$ requires C, 76.46; H, 8.11; N, 4.69; S, 10.74%); $[\alpha]_D^{22}$=−63.8 (*c* 1.3, $CHCl_3$); ν_{max} (film)/cm^{-1} 2957, 1494, 1454; δ_H (250 MHz; $CDCl_3$) 0.81 (6H, d, *J* 6.7, CH(C*H*$_3$)$_2$), 1.07 (6H, d, *J* 6.7, CH(C*H*$_3$)$_2$), 1.79–1.98 (2H, m, C*H*(CH$_3$)$_2$), 2.47–2.58 (2H, m C*H*CH(CH$_3$)$_2$), 2.77 (2H, dd, *J* 13.0, 5.2, CHC*H*αHβ), 3.02 (2H, dd, *J* 13.0, 6.4, CHCHα*H*β), 3.52 (4H, d, *J* 13.7, C*H*$_2$Ar), 3.66 (4H, d, *J* 13.7, C*H*$_2$Ar), 7.03–7.42 (20H, m, Ar); δ_C (63 MHz; $CDCl_3$) 20.6 (CH(*C*H$_3$)$_2$), 21.2 (CH(*C*H$_3$)$_2$), 29.6 (*C*H(CH$_3$)$_2$), 38.8 (S*C*H$_2$), 54.5 (Ar*C*H$_2$), 63.3 (*C*HCH(CH$_3$)$_2$), 126.9 (Ar), 128.2 (Ar), 129.1 (Ar), 140.0 (Ar); *m/z* (FAB) 597 (MH$^+$, 14%), 298 (50), 266 (14), 252 (100), 196 (7). (Found: M$^+$, 597.3340. $C_{38}H_{48}N_2S_2$ requires *M*, 597.3337.)

*6.38. Methyl-(*R*)-[*N-*phenyl-2-amino-2-phenyl]ethanoate* ***37***

Identical to the preparation of **7**, gave **37** (92%) as a white solid, mp 52°C (found: C, 74.67; H, 6.07; N, 5.79; $C_{15}H_{15}NO_2$ requires C, 74.67; H, 6.27; N, 5.80%); $[\alpha]_D^{22}$=−88.1 (*c* 2.1, $CHCl_3$); ν_{max} (film)/cm^{-1} 3403 (NH), 1737 (C=O), 1604, 1506, 1314, 1174; δ_H (250 MHz; $CDCl_3$) 3.74 (3H, s, OC*H*$_3$), 5.09 (1H, s, PhC*H*)), 6.54–6.75 (3H, m, Ar), 7.08–7.55 (7H, m, Ar); δ_C (63 MHz; $CDCl_3$) 52.8 (Ar*C*H), 60.7 (O*C*H$_3$), 113.4 (Ar), 118.1 (Ar), 127.3 (Ar), 128.3 (Ar), 128.9 (Ar), 129.3 (Ar), 137.6 (Ar), 146.0 (Ar), 172.3 (C=O); *m/z* (EI) 241 (M$^+$, 27%), 182 (100), 104 (17), 77 (28), 51 (10). (Found: M$^+$, 241.1196. $C_{15}H_{15}NO_2$ requires *M*, 241.1103.)

*6.39. Methyl-(*R*)-[*N*-formyl,*N*-phenyl-2-amino-2-phenyl]ethanoate*

Identical to the preparation of **13** with purification by column chromatography on silica eluting with ethyl acetate/light petroleum (40%) to afford the *N*-formyl,*N*-phenyl methyl ester (88%) as a mobile colourless oil (found: C, 71.04; H, 5.49; N, 5.09; $C_{16}H_{15}NO_3$ requires C, 74.67; H, 6.27; N, 5.80%); $[\alpha]_D^{22}=-38.4$ (*c* 2.5, $CHCl_3$); ν_{max} (film)/cm^{-1} 1748 (C=O), 1678 (C=O), 1595, 1494; δ_H (250 MHz; $CDCl_3$) 3.72 (3H, s, OC*H*$_3$), 6.11 (1H, s, C*H*Ph), 6.94–7.20 (10H, m, Ar), 8.29 (1H, s, C*H*O); δ_C (63 MHz; $CDCl_3$) 52.7 (Ar*C*H), 67.9 (O*C*H$_3$), 128.2 (Ar), 128.5 (Ar), 128.6 (Ar), 128.9 (Ar), 129.2 (Ar), 129.8 (Ar), 133.0 (Ar), 138.1 (Ar), 170.3 (C=O), 177 (C=O), 33.8 (*C*(CH$_3$)$_3$), 35.6 (N*C*H$_3$), 51.1 (*C*HC(*C*H$_3$)$_3$), 72.8 (O*C*H$_3$), 175.3 (C=O); *m/z* (EI) 269 (M$^+$, 41%), 237 (47), 210 (92), 182 (100), 104 (54), 77 (71). (Found: M$^+$, 269.0096. $C_{16}H_{15}NO_3$ requires *M*, 269.1052.)

*6.40. (*R*)-*N*-Formyl,*N*-phenyl-2-amino-2-phenylethan-1-ol* ***39***

Identical to the preparation of **14** except that the reaction mixture was refluxed for 3 hours and purification by column chromatography on silica eluting with ethyl acetate/light petroleum (30%) to afford **39** (462 mg, 98%) as a mobile colourless oil (found: C, 79.43; H, 7.56; N, 5.98; $C_{15}H_{17}NO$ requires C, 79.26; H, 7.54; N, 6.16%); $[\alpha]_D^{22}=-125.9$ (*c* 2.2, $CHCl_3$); ν_{max} (film)/cm^{-1} 3389 (OH), 1598, 1504; δ_H (250 MHz; $CDCl_3$) 2.78 (3H, s, NC*H*$_3$), 4.06–4.20 (2H, m, CH_2OH), 5.08 (1H, dd, *J* 8.2, 6.4, C*H*Ph), 6.28–7.28 (10H, m, Ar), 8.29 (1H, s, C*H*O); δ_C (63 MHz; $CDCl_3$) 28.4 (*C*H$_2$OH), 61.7 (NCH$_3$), 64.6 (Ar*C*H), 114.7 (Ar), 118.4 (Ar), 127.2 (Ar), 127.6 (Ar), 128.6 (Ar), 129.3 (Ar), 137.5 (Ar), 151.1 (Ar); *m/z* (EI) 227 (M$^+$, 12%), 196 (100), 180 (15), 91 (5), 77 (15). (Found: M$^+$, 227.1304. $C_{15}H_{17}NO$ requires *M*, 227.1310.)

*6.41. (*R*)-*N*-Methyl,*N*-phenyl-2-amino-2-phenyl-1-thiolacetylethane*

Identical to the preparation of **12** except the reaction mixture was stirred for an additional 1 hour at room temperature. Purification of the residue by column chromatography on silica eluting with ethyl acetate/light petroleum (5%) gave the *N*-methyl,*N*-phenyl thioacetate (76 mg, 92%) as a colourless oil (found: C, 71.34; H, 6.72; N, 5.09; S, 11.33; $C_{17}H_{19}NOS$ requires C, 71.54; H, 6.71; N, 4.91; S, 11.23%); $[\alpha]_D^{22}=-138.6$ (*c* 0.7, $CHCl_3$); ν_{max} (film)/cm^{-1} 1689, 1597, 1503; δ_H (250 MHz; $CDCl_3$) 2.31 (3H, s, COC*H*$_3$), 2.68 (3H, s, NC*H*$_3$), 3.48 (1H, dd, *J* 13.7, 9.3, C*H*αCHβS), 3.68 (1H, dd, *J* 13.7, 6.47, CHαC*H*βS), 5.14 (1H, dd, *J* 9.3, 6.4, ArC*H*), 6.73–6.90 (3H, m, Ar), 7.17–7.39 (7H, m, Ar); δ_C (63 MHz; $CDCl_3$) 30.6 (*C*H$_2$SCO), 31.1 (N*C*H$_3$), 32.1 (SCO*C*H$_3$), 61.2 (*C*HPh), 113.6 (Ar), 117.4 (Ar), 127.2 (Ar), 127.5 (Ar), 128.5 (Ar), 129.2 (Ar), 139.1 (Ar), 150.4 (Ar), 195.7 (C=O); *m/z* (EI) 285 (M$^+$, 15%), 196 (100), 180 (16), 77 (22). (Found: M$^+$, 285.1183. $C_{17}H_{19}NOS$ requires *M*, 285.1187.)

*6.42. (*R*)-*N*-Methyl,*N*-phenyl-2-amino-2-phenylethan-1-thiol* ***41***

A solution of the *N*-methyl,*N*-phenyl thioacetate (50 mg, 0.18 mmol), prepared above, in tetrahydrofuran (7 ml) was added to a stirred suspension of lithium aluminium hydride (27 mg, 0.7 mmol) at 0°C in diethyl ether (5 ml). The reaction mixture was left to stir at ambient temperature for 5 minutes and then quenched and worked up exactly as for the preparation of **1**. The crude product was redissolved in diethyl ether (6 ml) and filtered through a 2 cm pad of silica, the residue was washed with ethyl acetate/light petroleum (20%) and the combined organic layers were concentrated *in vacuo* to afford **41** (41 mg, 94%) as a colourless oil; $[\alpha]_D^{22}=-55.0$ (*c* 0.4, $CHCl_3$); ν_{max} (film)/cm^{-1} 2557 (SH), 1597, 1503; δ_H (250

MHz; $CDCl_3$) 1.43 (1H, dd, *J* 6.2 and 7.3, SH), 2.62 (3H, s, NC*H*$_3$), 3.02–3.14 (2H, m, C*H*αC*H*βS), 5.04 (1H, t, *J* 8.5, ArC*H*), 6.66–7.27 (10H, m, Ar); δ_C (63 MHz; $CDCl_3$) 28.7 (*C*H_2S), 30.5 (N*C*H_3), 58.2 (*C*HPh), 112.8 (Ar), 116.8 (Ar), 126.9 (Ar), 127.7 (Ar), 128.8 (Ar), 130.2 (Ar), 139.0 (Ar), 150.1 (Ar); *m/z* (EI) 243 (M^+, 35%), 196 (100), 137 (22), 77 (43). (Found: M^+, 243.1083. $C_{15}H_{17}NS$ requires *M*, 243.1081.)

6.43. (S)-N-*Phenyl*-tert-*leucine methyl ester* ***38***

Identical to the preparation of **7**, gave **42** (86%) as a white solid, mp 34–35°C (found: C, 70.67; H, 8.66; N, 6.07; $C_{13}H_{19}NO_2$ requires C, 70.56; H, 8.65; N, 6.33%); $[\alpha]_D^{22}=-106$ (*c* 3, $CHCl_3$); ν_{max} (film)/cm^{-1} 3404 (NH), 2960, 1732 (C=O), 1604; δ_H (250 MHz; $CDCl_3$) 1.08 (9H, s, C(C*H*$_3$)$_3$), 3.66 (3H, s, OC*H*$_3$), 3.82 (1H, s, C*H*C(CH$_3$)$_3$), 6.62–7.41 (5H, m, Ar); δ_C (63 MHz; $CDCl_3$) 26.7 (C(*C*H$_3$)$_3$), 34.5 (*C*(CH$_3$)$_3$), 51.5 (*C*HC(CH$_3$)$_3$), 65.5 (OCH$_3$), 113.8 (Ar), 118.4 (Ar), 129.3 (Ar), 175.1 (C=O); *m/z* (CI) 222 (MH^+, 100%), 164 (93), 150 (8), 104 (26), 77 (7). (Found: MH^+, 222.1491. $C_{13}H_{20}NO_2$ requires *M*, 222.1494.)

6.44. (S)-N-*Methyl*,N-*phenyl-2-amino-3,3-dimethylbutan-1-ol* ***40***

Identical to the preparation of **13** except that the final reaction mixture was heated at 60°C for 24 hours. The reaction mixture was then concentrated *in vacuo* to afford a colourless oil (255 mg) which was used directly without further purification.

Treatment with lithium aluminium hydride (181 mg, 4.73 mmol) under the same conditions as for the preparation of **14** except that the reaction mixture was refluxed for 3 hours. Gave **40** (90 mg, 51%) as a white solid, mp 98–100°C (light petroleum) (found: C, 70.67; H, 8.66; N, 6.07; $C_{13}H_{19}NO_2$ requires C, 70.56; H, 8.65; N, 6.33%); $[\alpha]_D^{22}=-58.3$ (*c* 2.5, $CHCl_3$); ν_{max} (film)/cm^{-1} 3335 (OH), 2954, 1597, 1504; δ_H (250 MHz; $CDCl_3$) 0.87 (9H, s, C(C*H*$_3$)$_3$), 2.81 (3H, s, NC*H*$_3$); 3.71–3.90 (3H, m, C*H*C(CH$_3$)$_3$ and C*H*$_2$OH), 6.63 (1H, t, *J* 7.5, Ar), 6.82 (2H, d, *J* 8.4, Ar), 7.15 (2H, dd, *J* 8.4, 7.5, Ar); δ_C (63 MHz; $CDCl_3$) 28.6 (C(*C*H$_3$)$_3$), 32.2 (*C*HC(CH$_3$)$_3$), 36.3 (*C*(CH$_3$)$_3$), 58.8 (*C*H$_2$OH), 68.1 (NCH$_3$), 113.5 (Ar), 117.1 (Ar), 129.2 (Ar), 150.9 (Ar); *m/z* (CI) 208 (M^+, 85%), 176 (16), 150 (100), 107 (16). (Found: M^+, 208.1709. $C_{13}H_{19}NO_2$ requires *M*, 208.1701.)

6.45. (S)-N-*Methyl*,N-*phenyl-2-amino-3,3-dimethyl-1-thiolacetylbutane*

Identical to the preparation of **12** except that the reaction mixture was stirred for an additional 1 hour at room temperature. The resulting homogeneous yellow solution was concentrated *in vacuo* to afford a yellow oil. Purification of the residue by column chromatography silica eluting with ethyl acetate/light petroleum (5%) gave the *N*-methyl,*N*-phenyl thioacetate (188 mg, 92%) as a colourless oil (found: C, 67.67; H, 8.66; N, 5.28; S, 12.10; $C_{15}H_{23}NOS$ requires C, 67.88; H, 8.73; N, 5.28; S, 12.08%); $[\alpha]_D^{22}=-49.2$ (*c* 1, $CHCl_3$); ν_{max} (film)/cm^{-1} 2960, 1689 (C=O), 1596, 1504, 1318; δ_H (250 MHz; $CDCl_3$) 1.02 (9H, s, C(C*H*$_3$)$_3$), 2.22 (3H, s, NC*H*$_3$), 2.80 (3H, s, COC*H*$_3$), 3.08 (1H, dd, *J* 14.0, 11.9, C*H*αCHβS), 3.37 (1H, dd, *J* 14.0, 3.7, CHαC*H*βS), 3.81 (1H, dd, *J* 11.9, 3.7, C*H*C(CH$_3$)$_3$), 6.54–6.70 (3H, m, Ar), 7.07–7.18 (2H, m, Ar); δ_C (63 MHz; $CDCl_3$) 28.3 (C(*C*H$_3$)$_3$), 28.9 (CH$_2$SCO), 30.6 (*C*HC(CH$_3$)$_3$), 32.6 (COCH$_3$), 38.0 (*C*(CH$_3$)$_3$), 64.2 (NCH$_3$), 112.3 (Ar), 116.1 (Ar), 129.0 (Ar), 151.4 (Ar), 196.5 (C=O); *m/z* (EI) 265 (M^+, 22%), 208 (100), 176, (28), 166 (49), 132 (20), 77 (16). (Found: M^+, 265.1498. $C_{15}H_{23}NOS$ requires *M*, 265.1500.)

*6.46. (*S*)-*N*-*Methyl*,*N*-*phenyl-2-amino-3,3-dimethylbutan-1-thiol* **42**

A solution of the *N*-methyl,*N*-phenyl thioacetate (70 mg, 0.26 mmol), prepared above, in tetrahydrofuran (7 ml) was added to a stirred suspension of lithium aluminium hydride (40 mg, 1.06 mmol) at 0°C in diethyl ether (7 ml). The reaction mixture was left to stir at ambient temperature for 5 minutes and then quenched and worked up exactly as for the preparation of **1**. The crude product was redissolved in diethyl ether (5 ml) and filtered through a 2 cm pad of silica, the residue was washed with ethyl acetate/light petroleum (30%) and the combined organic layers were concentrated *in vacuo* to afford **42** (52 mg, 89%) as a colourless oil; $[\alpha]_D^{22}=-44.0$ (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 2959, 2575 (SH), 1598, 1505, 1318; δ_H (250 MHz; $CDCl_3$) 0.90 (9H, s, $C(CH_3)_3$), 1.28 (1H, dd, *J* 9.9, 4.4, S*H*), 2.71 (1H, ddd, *J* 13.4, 9.9, 3.4, C*H*αCHβS), 2.78 (3H, s, NCH_3) 2.91 (1H, ddd, *J* 13.4, 11.3, 4.4, CHαC*H*βS), 3.80 (1H, dd, *J* 11.3, 3.4, C*H*$C(CH_3)_3$), 6.62–6.87 (3H, m, Ar), 7.10–7.23 (2H, m, Ar); δ_C (63 MHz; $CDCl_3$) 23.6 (CH_2SH), 28.5 ($C(CH_3)_3$), 32.0 ($N(CH_3)_2$), 38.1 ($C(CH_3)_3$), 68.5 ($CHC(CH_3)_3$), 112.5 (Ar), 116.3 (Ar), 129.0 (Ar), 152.1 (Ar); *m/z* (EI) 223 (M^+, 23%), 176 (28), 166 (100), 132 (27), 77 (15). (Found: M^+, 223.1390. $C_{13}H_{21}NS$ requires *M*, 223.1395.)

Acknowledgements

We would like to thank the EPSRC, Pfizer, SmithKline Beecham and the University of Sheffield for financial support, Mr. H. Adams for solving the X-ray crystal structure, Mr. A. Jones and Ms. J. Stanbra for measuring micro analytical data and Mr. S. Thorpe and Mr. N. Lewus for providing mass spectra. The loan of GC equipment from Dr. Varinder K. Aggarwal and the help of Dr. Elfyn Jones with GC is gratefully acknowledged.

References

1. For a recent review see Krause, N. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 283.
2. Anderson, J. C.; Harding, M. *Chem. Commun*. **1998**, 393.
3. Kitamura, M.; Mika, T.; Nakano, K.; Noyori, R. *Tetrahedron Lett.* **1996**, *37*, 5141.
4. Wendish, V.; Sewald, N. *Tetrahedron: Asymmetry*, **1997**, *8*, 1253.
5. Arnauld, T.; Barton, D. H. R.; Doris, E. *Tetrahedron* **1997**, *53*, 4137.
6. Barton, D. H. R.; Finet, J.-P.; Khamsi, J. *Tetrahedron Lett*. **1989**, *30*, 937.
7. (a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 1348. (b) Louie, J.; Hartwig, J. F. *Tetrahedron Lett*. **1995**, *36*, 3609. (c) Ma, D.; Yao, J. *Tetrahedron: Asymmetry* **1996**, *7*, 3075.
8. Karrer, P.; Portmann, P.; Suter, M. *Helv. Chim. Acta* **1948**, *31*, 1617.
9. Tomkinson, N. C. O. PhD Thesis, University of Sheffield, 1996.
10. Crystallographic data (excluding structure factors) for structure **11** reported in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-102395. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336-033; e-mail: deposit@chemcrys.cam.ac.uk).
11. Swingle, N. M.; Reddy, K. V.; Rossiter, B. E. *Tetrahedron* **1994**, *50*, 4455.
12. Volante, R. P. *Tetrahedron Lett.* **1981**, *22*, 3119.
13. Krishnamurthy, S. *Tetrahedron Lett*. **1982**, *33*, 3315.
14. (a) Nakagawa, I.; Hata, T. *Tetrahedron Lett*. **1975**, 1409. (b) Siedlecka, R.; Skarzewski, J. *Synlett* **1996**, 757.
15. Berry, M. B.; Craig, D. *Synlett* **1992**, 41.
16. Duréault, A.; Tranchepain, I.; Greck, C.; Depezay, J.-C. *Tetrahedron Lett.* **1987**, *28*, 3341.
17. Birkofer, L.; Ritter, A.; Goller, H. *Chem. Ber.* **1963**, *96*, 3289.
18. Brittain, J.; Gareau, Y. *Tetrahedron Lett*. **1993**, *34*, 3363.

19. Enantioselection quantified by ^{13}C NMR analysis of the diastereomeric products formed upon reaction of the product with (*R*,*R*)-(−)-2,3-butanediol. See Hiemstra, H.; Wynberg, H. *Tetrahedron Lett*. **1977**, 2183.
20. Zhou, Q.-L.; Pfaltz, A. *Tetrahedron* **1994**, *50*, 4467.
21. Villacorta, G. M.; Pulla Rao, C.; Lippard, S. J. *J. Am. Chem. Soc*. **1988**, *110*, 3175.
22. (a) Tamaru, Y.; Tanigawa, H.; Yamamoto, Y.; Yoshida, Z. *Angew. Chem., Int. Ed. Engl*. **1989**, *28*, 351. (b) Sibille, S.; Ratovelomanana, V.; Périchon, J. *J. Chem. Soc., Chem. Commun*. **1992**, 283. (c) Lipshulz, B. H.; Wood, R. M.; Tirado, R. *J. Am. Chem. Soc*. **1995**, *117*, 6126. (d) Reddy, C. K.; Devasagayaraj, A.; Knochel, P. *Tetrahedron Lett*. **1996**, *37*, 4495.
23. Gonzalez-Cameno, A. M.; Badia, D.; Esther, K. M. U.; Arriortua, I. M.; Solans, X. *Tetrahedron* **1994**, *50*, 1097.
24. Soai, K.; Hayasaka, T.; Ugajin, S.; Yokoyama, S. *Chem. Lett*. **1988**, 1571.
25. (a) Bolm, C.; Ewald, M. *Tetrahedron Lett*. **1990**, *31*, 5011. (b) Uemura, M.; Miyake, R.; Nakayama, K.; Hayashi, Y. *Tetrahedron: Asymmetry* **1992**, *3*, 713. (c) Asami, M.; Usui, K.; Higuchi, S.; Inoue, S. *Chem. Lett*. **1994**, 297. (d) de Vries, A. H. M.; Jansen, J. F. G. A.; Feringa, B. L. *Tetrahedron* **1994**, *50*, 4479. (e) de Vries, A. H. M.; Imbos, R.; Feringa, B. L. *Tetrahedron: Asymmetry* **1997**, *8*, 1467.
26. Kang, J.; Kim, J. B.; Kim, J. W.; Lee, D. *J. Chem. Soc., Perkin Trans. 2*, **1997**, 189.
27. (a) Hof, R. P.; Poelert, M. A.; Peper, N. C. M. W.; Kellogg, R. M. *Tetrahedron: Asymmetry* **1994**, *5*, 31. (b) Kang, J.; Won Lee, J.; In Kim, J. *J. Chem. Soc., Chem. Commun*. **1994**, 2009. (c) Rijnberg, E.; Jastrzebski, J. T. B. H.; Janssen, M. D.; Boersma, J.; van Koten, G. *Tetrahedron Lett*. **1994**, *35*, 6521. (d) Gibson, C. L. *Chem. Commun*. **1996**, 645. (e) Masaki, Y.; Satoh, Y.; Makihara, T.; Shi, M. *Chem. Pharm. Bull*. **1996**, *44*, 454. f) Nakano, H.; Kumagai, N.; Matsuzaki, H.; Kabuto, C.; Hongo, H. *Tetrahedron: Asymmetry* **1997**, *8*, 1391.
28. Determined by chiral GLC using a Chrompak™ CP-Cyclodex b column.
29. A positive optical rotation was obtained, indicating the (*R*)-enantiomer. Pickard, R. H.; Kenyon, J. *J. Chem. Soc*. **1914**, 1115.
30. Soai, K.; Ookawa, A.; Kabe, T.; Ogawa, K. *J. Am. Chem. Soc*. **1987**, *109*, 7111.
31. Ohfune, Y. *Chem. Lett*. **1998**, 441.
32. Chaloner, P. A.; Langadianou, E. *Tetrahedron Lett*. **1990**, *31*, 5185.
33. Kellog, R. M.; Hof, R. P. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1651.
34. Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl*. **1991**, *30*, 49.
35. Kang, J.; Kim, D. S.; Kim, J. I. *Synlett* **1994**, 842.
36. Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl*. **1991**, *30*, 49.
37. For example see: Bedeker, A. V.; Koroleva, E. B.; Anderson, P. G. *J. Org. Chem*. **1997**, *62*, 2518.
38. Anderson, J. C.; Siddons, D. C.; Smith S. C.; Swarbrick, M. E. *J. Org. Chem*. **1996**, *61*, 4820.
39. (a) Kauffman, G. B.; Teter, L. A. *Inorg. Synth*. **1963**, *7*, 9. (b) Linstrumelle, G.; Krieger, J. K.; Whitesides, G. M. *Org. Synth*. **1976**, *55*, 103.
40. Beaulieu, P. L.; Wernic, D. *J. Org. Chem*. **1996**, *51*, 3635.