Synthesis and application of ligands for the asymmetric addition of organolithium reagents to imines

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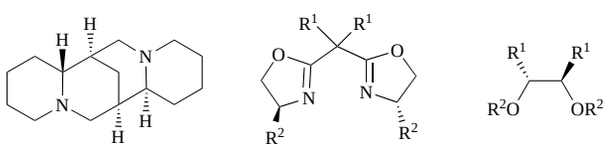
Amino acid derived ligands 4d,e are prepared from (*S*)-valine and (*S*)-proline respectively, and can be used as chiral ligands during the asymmetric addition of organolithium reagents to *N*-arylimines. Ligand 4e, which is prepared by two independent routes, is found to induce addition of organolithium reagents to the *si*-face of the imines, whilst ligand 4d in common with the previously reported catalysts 4a–c induces addition to the *re*-face of the imines.

Introduction

In recent years, considerable progress has been made in the asymmetric addition of carbon nucleophiles to prochiral carbonyl compounds under the influence of a chiral catalyst. In particular, the asymmetric catalysis of the addition of cyanide[1] (from hydrogen cyanide or trimethylsilyl cyanide) and the addition of organozinc reagents[2] to aldehydes and ketones have both been achieved with excellent asymmetric induction. By comparison, the asymmetric addition of carbon nucleophiles to prochiral imines leading to optically active amines is a field which is still in its infancy.[3] A number of chiral auxiliary based approaches have been reported,[4] but reports of asymmetric catalysts for this reaction are scarce. Compared to additions to carbonyl compounds, a number of additional factors need to be considered in the asymmetric addition of nucleophiles to prochiral imines. These include the lower electrophilicity of the carbon–nitrogen double bond compared to the carbonyl bond, the electronic and steric nature of the substituent on the nitrogen atom, and the possibility of *E*,*Z*-isomerism about the carbon–nitrogen double bond. The first of these factors can be an advantage, as the uncatalysed addition of nucleophiles to an imine will be retarded, but the second two points are complications.

Very recently, the first report of a catalytic, asymmetric Strecker reaction (addition of HCN to an imine) was reported,[5] and there are a handful of reports of catalysts for the addition of organolithium reagents to imines and their derivatives. In particular, sparteine[6,7] **1**, bis-oxazolines[6] **2**, *O*,*O*′-dialkyldihydrobenzoins[8,9] **3** and amino ethers[8–10] **4**, **5** have been employed as chiral catalysts and/or chiral ligands for this reaction. It is notable that structures **1**–**5** include both bi- and tridentate ligands, with examples of good and not so good asymmetric induction being reported in both cases. The catalytic, asymmetric addition of organometallic reagents to *N*-heteroatom substituted imines[7,11] and to nitrones[12] has also been reported.



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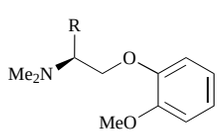

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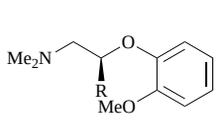

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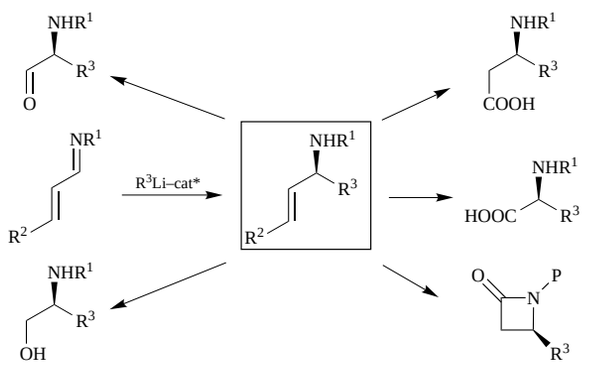
An attractive feature of this chemistry is the large number of natural products which contain a stereocentre adjacent to an amino group, and in particular by the ease with which enantiomerically pure allylic amines can be converted into α-amino acids, α-amino aldehydes, β-amino acids, β-lactams and β-amino alcohols (Scheme 1). However, catalysts **1**–**5** all suffer



Scheme 1

from one or more disadvantages as chiral catalysts, these include the availability of only one enantiomer, low levels of asymmetric induction, the need to use stoichiometric or greater amounts of the chiral species, and narrow substrate specificity. Thus, a research programme aimed at the development of more versatile catalysts for the asymmetric addition of organolithium reagents to imines was initiated within our group. In this paper, we report details of our results on the design of ligands analogous to compounds **4** for the asymmetric addition of organolithium reagents to α,β-unsaturated imines.[13]

Synthesis of chiral ligands

Of the chiral ligands **1**–**5**, those represented by structure **4** appeared to be a suitable starting point for our work. These ligands are readily prepared from (*S*)-amino acids and offer great scope for variation during optimisation studies. Three such catalysts **4a**–**c** have previously been reported,[8–10] each of which induces the addition of an organolithium reagent (methyllithium, butyllithium or vinyllithium) to the *re*-face of an *N*-(*p*-methoxyphenyl)imine as shown in Scheme 2. Ligands **4a**–**c**

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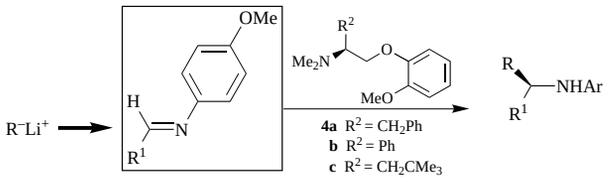


R = Me, Bu, $H_2C{=}CH$

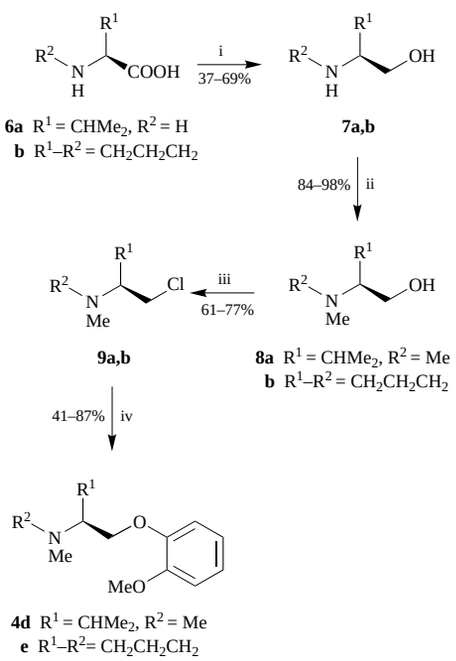
R^1 = Ph, PhCH=CH, 1-Naph, 2-Naph

Scheme 2

have been investigated in both stoichiometric (2.6 equiv.) and catalytic (0.05–0.3 equiv.) quantities, with higher enantiomeric excesses being obtained in the former case (42–77% *versus* 25–64%).

We decided to investigate the effect of further variation in the structure of the ligands, and chose to prepare ligands **4d** derived from (*S*)-valine, and **4e** derived from (*S*)-proline. Ligand **4d** offered the opportunity to investigate the effect of steric influences on the activity of the catalyst, whilst ligand **4e** being derived from a cyclic, secondary amino acid was anticipated to have fewer available conformations.

The synthesis of ligands **4d**,**e** was initially achieved from the corresponding amino acids using the route previously reported for ligands **4a**,**c**[9,14] as shown in Scheme 3. Thus reaction of (*S*)-



Scheme 3 *Reagents:* i, $NaBH_4$, H_2SO_4; ii, H_2CO, HCOOH; iii, $SOCl_2$; iv, *o*-$(MeO)C_6H_4OH$, NaH

valine **6a** or (*S*)-proline **6b** with sodium borohydride–conc. sulfuric acid[15] gave the corresponding amino alcohols **7a**,**b**. *N*,*N*-Dimethylation of **7a** and *N*-methylation of **7b** was achieved by treatment with formaldehyde and formic acid to give *N*-methylamino alcohols **8a**,**b**.[14] Chlorination of **8a**,**b** with thionyl chloride gave alkyl chlorides **9a**,**b**, which reacted with *o*-methoxyphenol in the presence of sodium hydride to give the desired ligands **4d**,**e** in overall yields of 19 and 45% from the commercially available amino alcohols respectively.

The spectral data for catalyst **4d** were entirely consistent with the proposed structure. For amino ether **4e** however, the ^1H NMR spectrum showed two singlets at 2.7 and 2.9 ppm corresponding to the *N*-methyl signal, and in the ^{13}C NMR spectrum [Fig. 1(*b*)] twice the expected number of resonances were observed. These extra peaks could have been due either to the presence of an impurity in the product, or to compound **4e** existing as two conformers interconverting slowly on the NMR

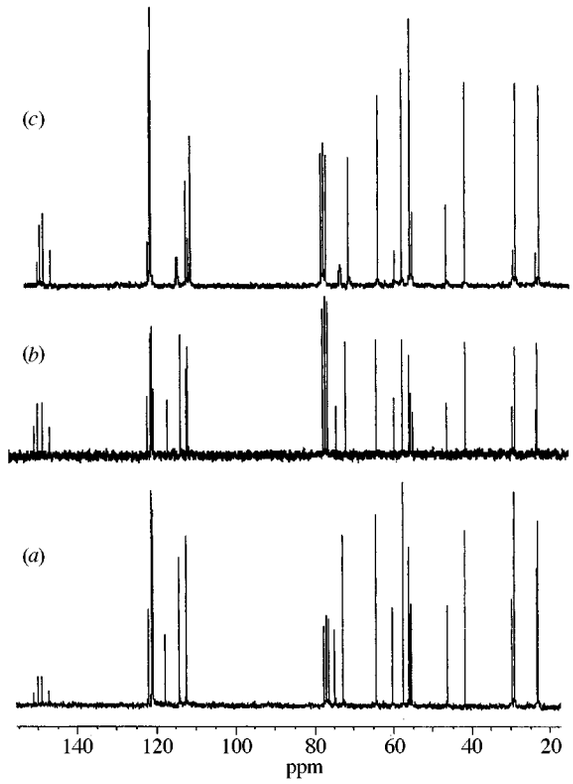
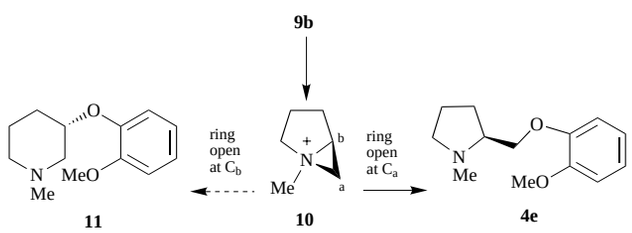


Fig. 1 ^{13}C NMR spectra of a mixture of compounds **4e** and **11** recorded at +55 °C (*a*), +20 °C (*b*) and −50 °C (*c*)

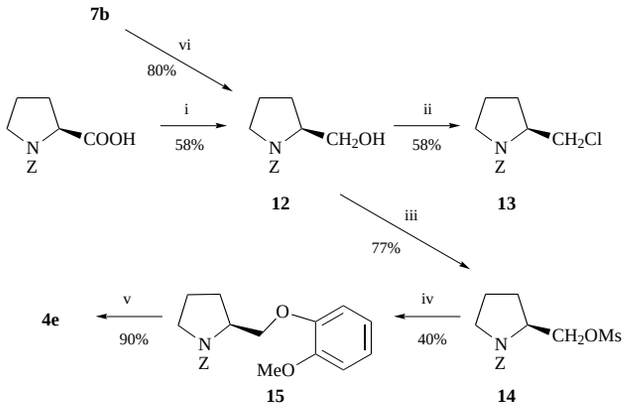
timescale. The former possibility appeared quite likely, since the final step of the synthesis will proceed *via* the aziridinium salt **10** as shown in Scheme 4. Ring opening of the aziridinium ring



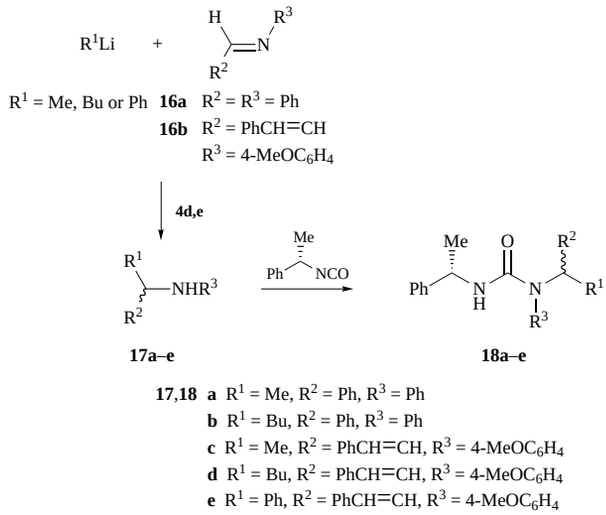
Scheme 4

of compound **10** could occur at two sites, leading to compounds **4e** and **11** respectively. A variable temperature ^{13}C NMR study [−50 to +55 °C Fig. 1(*a*)–(*c*)] showed that both the intensities and the chemical shifts of the ^{13}C resonances were temperature dependent. The changes in intensity of the peaks are quite noticeable in Fig. 1, and the largest change in chemical shift (2.0 ppm) is seen for the resonance corresponding to the CH_2O, which occurs at 70.6 ppm at −50 °C but at 72.6 ppm at +50 °C. This information strongly suggested that the appearance of multiple peaks in the NMR spectra of compound **4e** was due to the presence of two rotamers, as did the fact that capilliary GC analysis of compound **4e** gave a single peak.

To further investigate the possible presence of compound **11**, an alterative synthesis of catalyst **4e** was developed as shown in Scheme 5. Thus reduction of *N*-benzyloxycarbonylproline gave *N*-benzyloxycarbonylprolinol **12**, which could also be prepared by protection of amino alcohol **7b**. Reaction of alcohol **12** with thionyl chloride gave the chloropyrrolidine **13**, but this compound proved to be completely inert to substitution reactions under a range of reaction conditions. Alternatively, reaction of alcohol **12** with methanesulfonyl chloride gave the corresponding methenesulfonate **14** which did react with *o*-methoxyphenol in the presence of potassium *tert*-butoxide to give pyrrolidine **15**. It was expected that the presence of a benzyloxycarbonyl-



Scheme 5 *Reagents:* i, $NaBH_4$, H_2SO_4; ii, $SOCl_2$; iii, MsCl, Et_3N; iv, *o*-$(MeO)C_6H_4OH$, $KOCMe_3$; v, $LiAlH_4$; vi, ZONSu (Ms = $MeSO_2$; Z = $PhCH_2OCO$; Su = succinimide)



Scheme 6

protecting group on the pyrrolidine nitrogen would prevent the lone pair of electrons on nitrogen from being involved in this substitution reaction, and hence prevent the formation of rearranged products. Finally, reduction of compound **15** with lithium aluminium hydride again gave catalyst **4e**, though in this case only a single set of peaks were seen in the ^1H and ^{13}C NMR spectra of the catalyst. This synthesis thus proved that the literature approach to catalysts **4a**–**d** proceeds with approximately 30% rearrangement to compound **11** when applied to catalyst **4e**. The reason why the relative intensities and chemical shifts of the ^{13}C NMR signals of a mixture of compounds **4e** and **11** should be temperature dependent is not clear, but may be due to changes in the relaxation times, or to the formation of aggregates.

Asymmetric synthesis of amines

To test the catalytic activity of ligands **4d**,**e**, the addition of MeLi, BuLi and PhLi to imines **16a**,**b** was investigated as shown in Scheme 6, the results being presented in Table 1. It was found necessary to use toluene as a non-coordinating solvent, since in diethyl ether or THF much lower enantiomeric excesses were obtained. Under these reaction conditions, no addition of organolithium reagent to the imine occurred in the absence of ligands **4d**,**e**. The enantiomeric excess of the amines **17a**–**e** were determined by reaction with (*S*)-1-phenylethyl isocyanate to give ureas **18a**–**e**. The diastereomeric excesses of the ureas could conveniently be determined by integration of the ^1H NMR spectra, or by HPLC analysis. For each of amines **17a**–**e**, the corresponding racemic amine was also prepared (from imines **16a**,**b** omitting the chiral ligand **4d**,**e** and conducting the reactions at room temperature), and converted into the corresponding urea by reaction with (*S*)-1-phenylethyl isocyanate to provide a reference sample for diastereomeric excess determinations. In each case, the amine was also prepared using ligand **4a**,[8–10] so that the relative senses of asymmetric induction could be determined.

From the results given in Table 1, it can be seen that the presence of compound **11** has no effect upon the catalytic activity observed with catalyst **4e**. Thus comparison of entries 3, 4 and 10 with entries 12, 13 and 14 shows no significant differences. Interestingly however, the use of catalyst **4e** gave the opposite enantiomer (arising from addition of the organolithium reagent to the *si*-face of the imine) of amines **17** to that obtained using catalyst **4a**, despite the fact that both catalysts are derived from an (*S*)-amino acid. The magnitude of the enantiomeric excesses are however lower using catalyst **4e** than those reported for catalyst **4a**. Ligand **4d** however, was found to preferentially produce the same enantiomer of amines **17** as ligand **4a**, though again with a lower enantiomeric excess.

Conclusions

The synthesis of two new ligands (**4d** and **4e**) for the asymmetric addition of organolithium reagents to imines has been achieved. The synthesis of ligand **4e** by the standard procedure reported for similar ligands was found to produce approximately 30% of compound **11** as an inseparable by-product obtained due to neighbouring group participation in the final

Table 1 Addition of organolithium reagents to imines induced by ligands **4d**,**e**

Entry	Ligand (%)	R^1	R^2	R^3	Yield (%)	ee (%)	Configuration
1	**4d** (20)	Me	PhCH=CH	4-$MeOC_6H_4$	56	12	*R*
2	**4d** (20)	Bu	PhCH=CH	4-$MeOC_6H_4$	33	20	*a*
3	**4e** (25)	Me	PhCH=CH	4-$MeOC_6H_4$	42	10	*S*
4	**4e** (100)	Me	PhCH=CH	4-$MeOC_6H_4$	60	20	*S*
5	**4e** (200)	Me	PhCH=CH	4-$MeOC_6H_4$	42	21	*S*
6	**4e** (25)	Bu	PhCH=CH	4-$MeOC_6H_4$	50	12	*b*
7	**4e** (100)	Bu	PhCH=CH	4-$MeOC_6H_4$	40	5.5	*b*
8	**4e** (200)	Bu	PhCH=CH	4-$MeOC_6H_4$	37	1.5	*b*
9	**4e** (25)	Ph	PhCH=CH	4-$MeOC_6H_4$	51	13	*c*
10	**4e** (25)	Me	Ph	Ph	96	10	*S*
11	**4e** (25)	Bu	Ph	Ph	44	5.5	*c*
12	**4e**[d] (25)	Me	PhCH=CH	4-$MeOC_6H_4$	57	9	*S*
13	**4e**[d] (100)	Me	PhCH=CH	4-$MeOC_6H_4$	78	25	*S*
14	**4e**[d] (25)	Me	Ph	Ph	78	7.5	*S*

[a] Absolute configuration unknown, but shown to be the same as that obtained using catalyst **4a**. [b] Absolute configuration unknown, but shown to be the opposite to that obtained using catalyst **4a**. [c] Absolute configuration unknown. [d] Using ligand **4e** prepared by the route shown in Scheme 5 and so not contaminated with compound **11**.

S_N2 displacement reaction. An alternative synthesis of ligand **4e** circumventing this problem has been developed. Both ligands were found to be effective catalysts for the asymmetric addition of organolithium reagents to imines, and preferentially produced opposite enantiomers of the resulting amines though with relatively low enantiomeric excesses. The presence of compound **11** in the reaction mixture was shown to have no effect upon the catalytic activity of ligand **4e**.

At this stage, the reason for the difference in asymmetric induction observed using ligands **4d** and **4e** is not clear. Both catalysts are likely to be tridentate, however it appears that the conformationally constrained pyrrolidine ring of ligand **4e** occupies different space to the acyclic amino acid sidechains. This difference in occupied space around the lithium ion may well be the cause of the reversal of sense of asymmetric induction, as it may alter the way in which the organolithium reagent–chiral ligand complex and imine interact. Any more detailed proposal would be unduly speculative in the absence of information on the structure of the organolithium–ligand complexes. Our work in this area is continuing, focusing on the synthesis of new ligands related to compounds **4**, but capable of producing amines with higher enantiomeric excesses. This work will be reported in due course.

Experimental

^{1}H NMR spectra were recorded at 250 MHz on a Brucker AM250 spectrometer fitted with a ^{1}H–^{13}C dual probe, and were recorded at 293 K in $CDCl_3$ unless otherwise stated. Spectra were internally referenced either to TMS or to the residual solvent peak, and peaks are reported in ppm downfield of TMS. Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), some combination of these, broad (br) or multiplet (m). *J* Values are given in Hz. ^{13}C NMR spectra were recorded at 62.5 MHz on the same spectrometer as ^{1}H NMR spectra, at 293 K and in $CDCl_3$ unless otherwise stated. Spectra were referenced to the solvent peak, and are reported in ppm downfield of TMS. Peak assignments were made by DEPT editing of the spectra. Infrared spectra were recorded on a Perkin Elmer 1600 series FTIR spectrometer, only characteristic absorptions are reported, and peaks are reported as strong (s), moderate (m), weak (w) or broad (br). Mass spectra were recorded using the FAB technique (Cs^+ ion bombardment at 25 kV) on a VG Autospec spectrometer, or by chemical ionisation (CI) with ammonia on either a VG model 12-253 quadrupole spectrometer or a VG Quattro II triple quadrupole spectrometer. Only significant fragment ions are reported, and only molecular ions are assigned. High resolution mass measurements were made on a VG ZAB-E spectrometer. Optical rotations ($[\alpha]_D$) were recorded on an Optical Activity Ltd. Polar 2001 polarimeter, and are reported in units of 10^{-1} deg cm^2 g^{-1} along with the solvent and concentration in g per 100 ml. Melting points are uncorrected. Elemental analyses were performed within the Chemistry department on a Carolo Erba Model 1106 or Model 1108 analyser.

Analytical HPLC was carried out on a Waters HPLC system using a Regis *R,R* WHELKO-1 chiral stationary phase and detection by UV absorption at 254 nm. A solvent system of isopropyl alcohol (IPA)–hexane at a flow rate of 2.0 ml min^{-1} was used. Flash chromatography[16] was carried out on 40–60 μm mesh silica, thin layer chromatography was carried out on aluminium backed silica plates (0.25 mm depth of silica containing UV254), and the plates were visualised with UV light, and/or dodecaphosphomolybdic acid as appropriate.

All yields refer to isolated, purified material, and are unoptimised. THF and diethyl ether were dried by distillation from sodium immediately prior to use. Toluene was dried over sodium wire. Other solvents were used as supplied. Ether refers to diethyl ether. Petrol refers to the fraction of light petroleum with bp 40–60 °C.

(2*S*)-1-(*o*-Methoxyphenoxy)-2-dimethylamino-3-methylbutane 4d

o-Methoxyphenol (16.0 g, 0.13 mol) was added to a suspension of NaH (3.0 g, 0.125 mol) in DMF (20 ml) at 0 °C. The mixture was stirred at room temperature for 40 min, then a solution of (2*S*)-1-chloro-2-dimethylamino-3-methylbutane hydrochloride[17] **9a** (4.9 g, 0.033 mol) in DMF (165 ml) was added. The mixture was stirred at room temperature for 24 h, then concentrated to approximately 30 ml, diluted with water (80 ml) and extracted with ether (3 × 80 ml). The combined organic extracts were washed successively with 10% aq. NaOH, water and brine, and dried over K_2CO_3. Concentration *in vacuo* afforded catalyst **4d** (3.2 g, 41%) as a slightly pink oil, $[\alpha]_D^{20}$ +2.8 (*c* 1.0, EtOH); ν_{max}(film)/cm^{-1} 3150w, 2957s, 1677s and 1594m; δ_H 0.90 (3H, d, *J* 6.7, CH_3), 1.00 (3H, d, *J* 6.7, CH_3), 2.03 (1H, octet, *J* 6.7, Me_2CH), 2.37 (6H, s, NMe_2), 2.45–2.55 (1H, m, NCH), 3.79 (3H, s, OCH_3), 4.12 (2H, d, *J* 4.6, OCH_2) and 6.85–6.95 (4H, m, Ph); δ_C 19.78 (q), 21.00 (q), 28.19 (d), 42.05 (q), 56.06 (d), 66.50 (t), 68.87 (q), 112.23, 113.49, 120.86 and 121.07 (d), 148.57 and 149.81 (s); *m/z* (EI) 237 (M^+, 14%) and 194 (100) (Found: M^+, 237.1729. $C_{14}H_{23}NO_2$ requires *M*, 237.1729).

(2*S*)-*N*-Methyl-2-(*o*-methoxyphenoxymethyl)pyrrolidine 4e, route A

The above method was followed using: sodium hydride (12.0 g of 60% dispersion in oil, 0.30 mol), DMF (440 ml), 2-methoxyphenol (32 ml, 36.1 g, 0.30 mol) and (2*S*)-*N*-methyl-2-chloromethylpyrrolidine hydrochloride[17] **9b** (11.84 g, 0.070 mol). The product was distilled under reduced pressure (0.5 mmHg, 130 °C) to give compound **4e** as a clear oil (13.4 g, 87%). Analytical data are given in route B.

(2*S*)-*N*-Benzyloxycarbonyl-2-methylsulfonyloxypyrrolidine 14

Methanesulfonyl chloride (0.37 g, 0.25 ml, 3.2 mmol) was added to a stirred solution of (*S*)-*N*-benzyloxycarbonylprolinol[15] **12** (0.5 g, 2.1 mmol) and triethylamine (0.32 g, 3.2 mmol) in CH_2Cl_2 (50 ml), and the solution stirred overnight. The reaction was washed with 2 M aq. HCl (40 ml), 5% aq. K_2CO_3 (40 ml) and water (40 ml), then the organic phase was dried over $MgSO_4$ before filtering and evaporating solvent *in vacuo*. A brown oil was obtained which was purified by flash chromatography (hexane–EtOAc, 1:1). The desired product **14** (0.51 g, 77%) was obtained as a clear oil, $[\alpha]_D^{26}$ −54.4 (*c* 1.7, $CHCl_3$); ν_{max}(film)/cm^{-1} 3030w, 2959m, 1734m, 1701s, 1413s, 1357s and 1175s; δ_H 1.9–2.1 [4H, m, $(CH_2)_2$], 2.8 and 2.9 (3H, 2 × s, CH_3SO_2), 3.4–3.5 (2H, m, CH_2N), 4.1–4.4 (3H, m, CH_2O + NCH), 5.2 (2H, s, CH_2Ph) and 7.3–7.4 (5H, m, C_6H_5); δ_C 22.9 and 23.7 (t), 27.7 and 28.5 (t), 36.8 (q), 46.8 and 47.1 (t), 55.6 and 56.3 (d), 66.8 and 67.1 (t), 69.3 and 69.5 (t), 127.8, 128.0, 128.2 and 128.5 (d), 136.4 and 136.7 (s) and 154.9 (s); the multiple peaks in the ^{1}H and ^{13}C NMR spectra were due to the presence of rotamers about the urethane amide bond; *m/z* (CI, NH_3) 314 (MH^+, 25%), 218 (45), 145 (85) and 84 (100) (Found: MH^+, 314.1062. $C_{14}H_{20}NO_5S$ requires *M*, 314.1062).

(2*S*)-*N*-Benzyloxycarbonyl-2-(*o*-methoxyphenoxymethyl)-pyrrolidine 15

To a solution of potassium *tert*-butoxide (4.10 g, 36.5 mmol) in dry *tert*-butyl alcohol (40 ml) was added a solution of 2-methoxyphenol (4.53 g, 36.5 mmol) in *tert*-butyl alcohol (40 ml) followed by a solution of (2*S*)-*N*-benzyloxycarbonyl-2-methylsulfonyloxypyrrolidine **14** (2.86 g, 9.12 mmol) in *tert*-butyl alcohol (40 ml). The reaction was heated to reflux overnight before concentration *in vacuo* and dilution with EtOAc (100 ml). The solution was washed with 2 M aq. HCl (100 ml), water (100 ml) and brine (100 ml), and then dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an orange oil. This was purified by flash chromatography (hexane–EtOAc, 4:1) to give compound **15** (2.22 g, 71%) as a colourless oil, $[\alpha]_D^{20}$ −40.0 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 3063m, 2953s, 1697s, 1505s, 1454s,

1410s and 1253s; δ_H 1.8–2.1 [4H, m, $(CH_2)_2$], 3.3–3.5 (2H, m, CH_2N), 3.8 (3H, s, OCH_3), 4.0–4.1 (1H, m, CH), 4.1–4.2 (2H, m, CH_2O), 5.1 (2H, s, CH_2Ph), 6.8–6.9 (4H, m, $C_6H_4OCH_3$) and 7.2–7.3 (5H, m, C_6H_5); δ_C 22.7 and 23.7 (t), 28.0 and 28.7 (t), 46.7 and 47.1 (t), 56.0 (q), 55.7 and 56.4 (d), 66.7 and 67.1 (t), 68.5 and 69.0 (t), 113.4, 113.5, 120.1, 127.8, 128.1 and 128.5 (d), 136.6, 136.9, 148.1 and 148.5 (s), 154.9 and 155.1 (s); *m/z* (CI, NH_3) 342 (MH^+, 90%), 208 (70), 84 (100) (Found: M^+, 342.1705. $C_{20}H_{24}NO_4$ requires *M*, 342.1705).

(2*S*)-*N*-Methyl-2-(*o*-methoxyphenoxymethyl)pyrrolidine 4e, route B

$LiAlH_4$ (0.02 g, 0.52 mmol) was added to a stirring solution of compound **15** (52 mg, 0.15 mmol) in dry THF (10 ml) at 0 °C and the mixture was heated under reflux for 2 h. The reaction was cooled to room temperature and diluted with EtOAc (2 ml) followed by water (20 ml), acidified to pH 3 using 2 M aq. HCl, and washed with ether (2 × 20 ml). The aqueous layer was basified (pH 10) using 2 M aq. NaOH and extracted with EtOAc (2 × 20 ml), the EtOAc extracts were combined and dried over $MgSO_4$ prior to filtering and removing solvent *in vacuo*. Compound **4e** (30 mg, 90%) was obtained as a colourless oil, $[\alpha]_D^{26}$ −38.4 (*c* 1.1, $CHCl_3$); ν_{max}(film)/cm^{-1} 2938s, 2779s, 1592s and 1505s; δ_H 1.7–1.9 [3H, m, $(CH_2)_2$], 2.1–2.2 [1H, m, $(CH_2)_2$], 2.4–2.5 (1H, m, CH_2N), 2.6 (3H, s, CH_3N), 3.0 (1H, pseudo quintet, *J* 6.6, NCH), 3.3–3.4 (1H, m, CH_2N), 3.9 (3H, s, CH_3O), 4.0 (1H, dd, *J* 5.6, 9.8, CH_2O), 4.2 (1H, dd, *J* 5.7, 9.7, CH_2O) and 6.9–6.95 (4H, m, $C_6H_4OCH_3$); δ_C 22.6 (t), 28.6 (t), 41.1 (q), 55.9 (q), 57.2 (t), 64.5 (d), 71.1 (t), 112.0, 113.8, 120.9 and 121.5 (d), 148.3 and 149.6 (s); *m/z* (EI) 221 (M^+, 3%) and 84 (100) [Found: (CI, NH_3) MH^+, 222.1494. $C_{13}H_{20}NO_2$ requires *M*, 222.1495].

General procedure for the asymmetric alkylation of imines using organolithium reagents

A solution of the appropriate organolithium reagent (BuLi, MeLi or PhLi) (3.0 mmol) was added to a stirred solution of imine **16a**,**b** (2.0 mmol) and chiral ligand **4d**,**e** (0.5 to 4.0 mmol) in toluene (70 ml) at −78 °C under a nitrogen atmosphere. The solution was stirred at this temperature for 3 h and subsequently at −50 °C for 3 h, before quenching with water (20 ml). The reaction mixture was washed with 5% aq. K_2CO_3 and the aqueous layer back extracted with EtOAc. The combined organic extracts were again washed with water and brine before being dried over K_2CO_3 and evaporated *in vacuo* to leave an orange residue which was purified by flash chromatography to give amines **17a**–**e**.

General procedure for the preparation of ureas 18a–e

To a solution of amine **17a**–**e** (20–50 mg) in $CDCl_3$ (0.5 ml) was added (*S*)-1-phenylethyl isocyanate (15 μl, 18 mg, 0.23 mmol). The resulting solution was allowed to stand at room temperature for 24 h to enable the reaction to reach completion, before analysis of ureas **18a**–**e** by ^{1}H NMR spectroscopy and HPLC without purification. If unreacted amine was detected by ^{1}H NMR, then a further batch of isocyanate was added and the solution again allowed to stand for 24 h before analysis. No evidence of any kinetic resolution was observed during this derivatisation, and all of the amine **17a**–**e** was consumed (as judged by ^{1}H NMR) before any analysis of the enantiomeric excess was undertaken.

1-Phenylamino-1-phenylethane 17a[18]

The general procedure was followed using ligand **4e**, and the product was purified by flash chromatography (petrol–Et_2O, 5:1) to give amine **17a** in 96% yield, $[\alpha]_D^{24}$ +0.80 (*c* 1.0, EtOH); ν_{max}(film)/cm^{-1} 3409m, 3082m, 2968s, 1600s, 1505s and 1318s; δ_H 1.5 (3H, d, 6.7, CH_3), 4.0–4.2 (1H, br s, NH), 4.5 (1H, q, *J* 6.7, $CHCH_3$), 6.5 (2H, d, *J* 7.6, NC_6H_5), 6.6 (1H, t, *J* 7.3, NC_6H_5), 7.1 (2H, t, *J* 7.9, NC_6H_5) and 7.2–7.5 (5H, m, C_6H_5). The corresponding urea **18a** was prepared following the general procedure, δ_H 1.3 (3H, d, *J* 6.9, CH_3), 1.4 (3H, d, *J* 7.2, CH_3), 4.2 (1H, d, *J* 7.4, NH), 5.1 (1H, q, *J* 7.0, $CHCH_3$), 6.1 (1H, 2 × q, 7.1, $CHCH_3$), 6.8 (2H, m, NC_6H_5) and 7.1–7.4 (13H, m, C_6H_5); enantiomeric excess 12%; chiral HPLC, hexane–IPA, 3:2, 3.03 min (17%), 4.05 min (22%), 12.8% ee; absolute configuration (*S*).

1-Phenylamino-1-phenylpentane 17b[10]

The general procedure was followed using ligand **4e**, and the product was purified by flash chromatography (petrol–Et_2O, 20:1) to give amine **17b** in 44% yield, $[\alpha]_D^{23}$ +0.90 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 3412m, 3051m, 2954s, 1600s, 1502s and 1317s; δ_H 0.75 (3H, t, *J* 7.0, CH_3), 1.0–1.3 [4H, m, $(CH_2)_2$], 1.5–1.7 (2H, m, CH_2), 3.8–4.0 (1H, br s, NH), 4.15 (1H, t, *J* 6.8, CH), 6.4 (2H, d, *J* 7.6, NC_6H_5), 6.5 (1H, t, *J* 7.3, NC_6H_5), 7.0 (2H, t, *J* 7.9, NC_6H_5) and 7.1–7.3 (5H, m, C_6H_5). The corresponding urea **18b** was prepared following the general procedure and analysed by chiral HPLC, hexane–IPA, 9:1, 5.64 min (46%), 6.43 min (41%), 5.7% ee.

3-[(*p*-Methoxyphenyl)amino]-1-phenylbut-1-ene 17c[10]

The general procedure was followed using ligand **4d** or **4e**, and the product was purified by flash chromatography (petrol–Et_2O, 5:1), giving amine **17c** as a yellow oil in 42% yield, $[\alpha]_D^{25}$ −29.5 (*c* 1.0, $CHCl_3$) using ligand **4e**; $[\alpha]_D^{20}$ +20.5 (*c* 2.6, $CHCl_3$) using ligand **4d**; ν_{max}(film)/cm^{-1} 3394m, 3055m, 2964s, 1616m, 1511s and 1448s; δ_H 1.45 (3H, d, *J* 6.6, CH_3), 3.2–3.6 (1H, br s, NH), 3.8 (3H, s, OCH_3), 4.1 (1H, quintet, *J* 6.2, CH), 6.25 (1H, dd, *J* 5.9, 15.9, C*H*=CHPh), 6.6 (1H, d, *J* 15.5, CH=C*H*Ph), 6.65 (2H, d, *J* 8.9, $C_6H_4OCH_3$), 6.8 (2H, d, *J* 8.9, $C_6H_4OCH_3$) and 7.2–7.4 (5H, m, C_6H_5). The corresponding urea **18c** was prepared following the general procedure, δ_H 1.2 (3H, 2 × d, *J* 6.9, CH_3), 1.35 (3H, 2 × d, *J* 6.9, CH_3), 3.85 (3H, s, OCH_3), 4.25 (1H, d, *J* 7.8, NH), 5.0 (1H, m, $CHCH_3$), 5.5 (1H, quintet, *J* 6.7, $CHCH$=CH), 6.2 (1H, dd, *J* 6.5, 15.9, C*H*=CHPh), 6.5 (1H, d, *J* 15.9, CH=C*H*Ph), 6.9 (2H, d, *J* 8.8, $C_6H_4OCH_3$), 7.1 (2H, d, *J* 8.8, $C_6H_4OCH_3$) and 7.15–7.4 (10H, m, C_6H_5). Enantiomeric excess 12% in favour of the (*R*)-enantiomer using ligand **4d** and 19% in favour of the (*S*)-enantiomer using ligand **4e**. Chiral HPLC, hexane–IPA, 1:1, 4.33 min (58%), 13.45 min (35%), 25% ee using ligand **4e**.

3-[(*p*-Methoxyphenyl)-1-phenylhept-1-ene 17d[10]

The general procedure was followed using ligand **4d** or **4e**, and the product was purified by flash chromatography (petrol–Et_2O, 6:1) to give amine **17d** in 40% yield, $[\alpha]_D^{24}$ −1.8 (*c* 1.0, $CHCl_3$) using ligand **4e**, $[\alpha]_D^{20}$ 7.2 (*c* 1.0, $CHCl_3$) using ligand **4d**; ν_{max}(film)/cm^{-1} 3398m, 3056s, 2928s, 1617m, 1517s and 1463s; δ_H 0.95 (3H, t, *J* 6.8, CH_3), 1.3–1.6 [4H, m, $(CH_2)_2$], 1.6–1.8 (2H, m, CH_2), 3.3–3.4 (1H, br, NH), 3.75 (3H, s, OCH_3), 3.9 (1H, q, *J* 6.5, NCH), 6.15 (1H, dd, *J* 6.5, 15.9, C*H*=CHPh), 6.55 (1H, d, *J* 15.9, PhC*H*=CH), 6.6 (2H, d, *J* 9.0, $C_6H_4OCH_3$), 6.8 (2H, d, *J* 8.9, $C_6H_4OCH_3$) and 7.2–7.5 (5H, m, C_6H_5). The corresponding urea **18d** was prepared following the general procedure, and analysed by chiral HPLC, hexane–IPA, 2:3, 4.09 min (49%), 6.22 min (44%), 5.4% ee. Absolute configuration was not assigned, however the configuration using ligand **4e** is the opposite to that obtained using catalyst **4a**.

3-[(*p*-Methoxyphenyl)amino]-1,3diphenylprop-1-ene 17e[10]

The general procedure was followed, and the product was purified by flash chromatography (petrol–EtOAc, 6:1) to yield amine **17e** in 51% yield, $[\alpha]_D^{18}$ −3.7 (*c* 1.0, $CHCl_3$); ν_{max}(CH_2Cl_2)/cm^{-1} 3399m, 3025s, 2830s, 1598s and 1510m; δ_H 3.75 (3H, s, OCH_3), 3.8–4.0 (1H, br s, NH), 5.05 (1H, d, *J* 6.3, NCH), 6.4 (1H, dd, *J* 6.2, 15.8, C*H*=CHPh), 6.6 (3H, m, CH=C*H*Ph, $C_6H_4OCH_3$), 6.85 (2H, d, *J* 8.9, $C_6H_4OCH_3$) and 7.2–7.5 (10H, m, C_6H_5). The corresponding urea **18e** was prepared following the general procedure, δ_H 1.3 (3H, d, *J* 6.9, CH_3), 3.8 (3H, s, OCH_3), 4.4 (1H, d, *J* 7.8, NH), 5.1 (1H, quintet, *J* 7.5,

C*H*CH_3), 6.3 (1H, dd, *J* 8.5, 15.7, C*H*=CHPh), 6.5 (1H, d, *J* 8.6, CH), 6.7 (1H, d, *J* 15.9, CH=C*H*Ph), 6.8–7.0 (4H, m, $C_6H_4OCH_3$) and 7.2–7.5 (15H, m, C_6H_5); enantiomeric excess 11%; chiral HPLC, hexane–IPA, 3:2, 6.52 min (45%), 10.32 min (35%), 12.5% ee.

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