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Development of new camphor based N,S chiral ligands and their application in transfer hydrogenation †

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A new class of N,S-containing chiral compounds based on the camphor scaffold have been synthesised and evaluated as chiral catalysts in the transfer hydrogenation of acetophenone. The best results were achieved using compound **6a** as the ligand and $[Ir(COD)Cl]_2$ as the metal precursor.

Introduction

Sulfur-containing ligands have been widely used in asymmetric catalyses.[1] The sulfur moiety creates additional possibilities compared to nitrogen- and oxygen-containing ligands since sulfur can become chiral when coordinated to a metal. N,S-Chelating ligands have been studied in a variety of reactions such as allylic alkylation,[2,3] hydrogenation,[4] diethyl zinc addition,[5] and conjugate addition to enones.[6]

Asymmetric transfer hydrogenation of prochiral ketones is a very attractive method for the enantioselective synthesis of optically active secondary alcohols due to the relatively mild conditions and the advantageous use of isopropyl alcohol or formic acid as a hydrogen source. This transformation has been extensively studied[7] but surprisingly only a few examples involve a sulfur-containing ligand. The most relevant examples are the works of Lemaire,[8] van Leeuwen[9] and Andersson.[10] Until now none of the amino-sulfur ligands has been able to match the results achieved with amino-alcohol in terms of activity and selectivity.

In the pharmaceutical and chemical industries there is a big demand for new chiral ligands that are readily available, are cheap and can perform catalysis with very high activity and selectivity. In this context the chiral pool is a very good source of cheap and highly chiral molecules. Here we report on the preparation of two series of N,S-ligands (Fig. 1) and their evaluation in the transfer hydrogenation of acetophenone using 2-propanol as the hydrogen donor and $[Ir(COD)Cl]_2$ as the catalyst precursor (Scheme 1). The ligands were prepared using a simple five-step synthesis starting from commercially available camphorsulfonic acid in its enantiopure form. We decided to focus on the cheaper (*S*) form but it is important to note that both enantiomeric forms of the ligands can be prepared using the same methodology. Using a novel synthetic protocol the two series of ligands could be synthesised by simply modifying the last step from a stereoselective reduction to a Beckmann rearrangement. Ligands **6a**–**d** have an exocyclic primary amine moiety while ligands **7a**–**f** contain an intracyclic secondary amine yielding either a 1,3 or a 1,2 relationship between the sulfur and the nitrogen atom, leading to a five- (ligands **6a**–**d**) or six- (ligands **7a**–**f**) membered chelate on complexation with a metal.

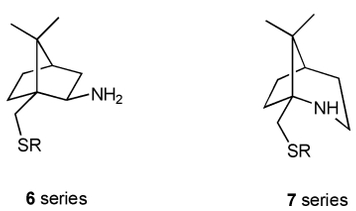
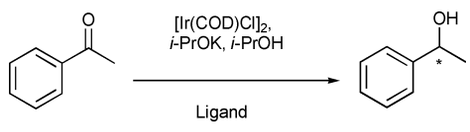


Fig. 1 The two series of N,S-ligands.



Scheme 1 Asymmetric transfer hydrogenation of acetophenone.

Results and discussion

Synthesis of the chiral ligands

Commercially available camphorsulfonic acid (*S*)-**1** was refluxed in thionyl chloride according to a literature procedure[11] to give camphorsulfonyl chloride **2** in quantitative yield, which was then reduced in presence of an excess of triphenylphosphine to obtain compound **3** in good yield. Subsequent alkylation of the thiol functionality using a range of alkyl halides and sodium hydride as a base led to thioethers **4a**–**d**. Because of the low reactivity of non-activated aryl halides towards thiols, the phenyl derivative **4e** was prepared using a palladium-catalysed reaction. The ketone functionality was transformed to an oxime group using hydroxylamine to produce compounds **5a**–**f** that are key intermediates to both ligands series (Scheme 2).

Many different reaction conditions have been reported for the reduction of the oxime moiety. The most satisfactory one due to its high stereocontrol involves a mixture of nickel(II) chloride and sodium borohydride. Using this protocol, compounds **5a**–**d** were transformed with very good stereoselectivity to the primary amines **6a**–**d** having the nitrogen in the equatorial position.[12] Attempts to prepare compounds **6a**–**d** using direct reductive amination of ketones **4a**–**e** were unsuccessful due to poor stereoselectivity. If oximes **5a**–**f** are instead treated with DIBAL they undergo a Beckmann rearrangement followed by reduction of the amide functionality to produce the secondary amines **7a**–**f** having intramolecular nitrogen (Scheme 3).

Amination of compound **6a** by treatment with formamide followed by reduction with lithium aluminium hydride gave ligand **8a**, which has a methyl substituted secondary amine. Compound **9a** bearing a benzyl-substituted imine was synthesised in good yield by condensation of the ketone **4a** with benzylamine.

Evaluation of the ligands in asymmetric transfer hydrogenation

Previous work on N,S-ligands[13] has shown that the most efficient pre-catalyst for transfer hydrogenation is $[Ir(COD)Cl)]_2$. The ligands were therefore evaluated in the reduction of

† Electronic supplementary information (ESI) available: ^{13}C NMR spectra. See http://www.rsc.org/suppdata/ob/b4/b402805h/

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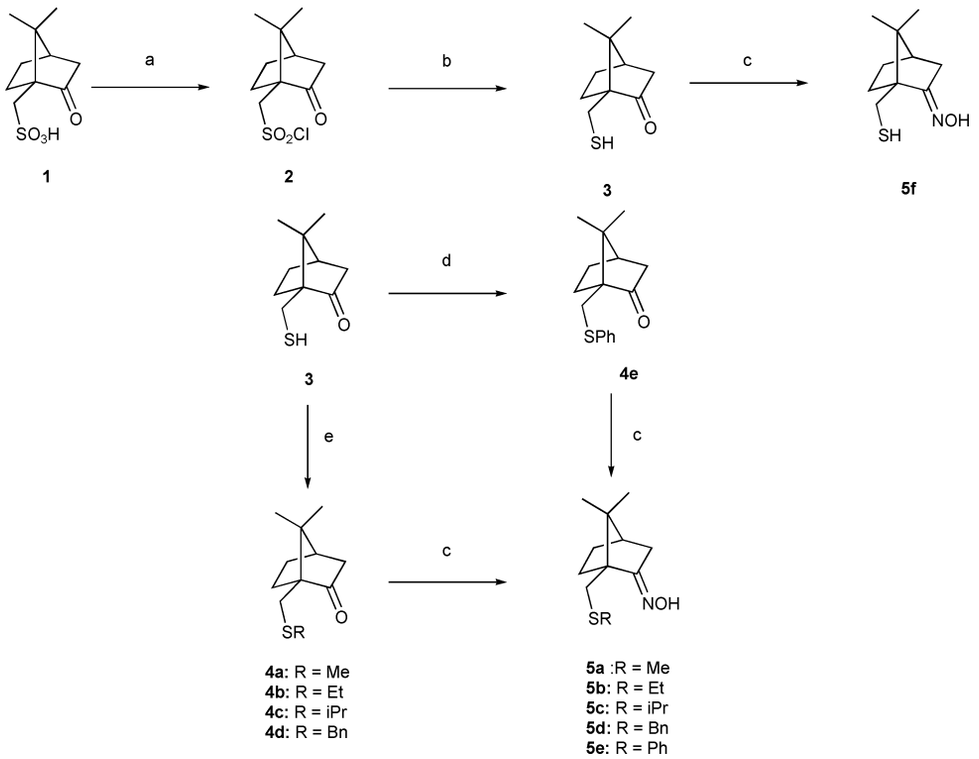
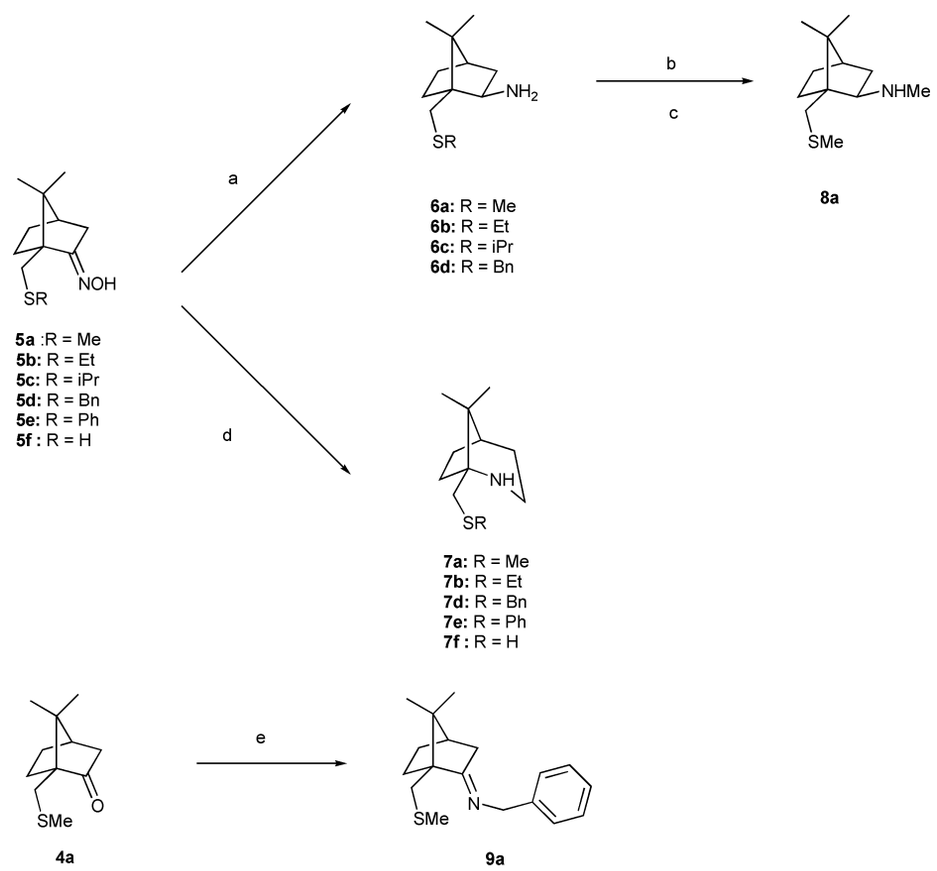


Scheme 2 Synthesis of the key intermediates **5a**–**f**. a) $SOCl_2$, reflux, 2 h; b) 3 equiv. PPh_3, H_2O–1,4-dioxane (1 : 4), reflux 2 h; c) 3 equiv. pyridine, 5 equiv. NH_2OH-HCl, ethanol 96%, reflux overnight; d) 2 equiv. EtONa, EtOH, 1.1 equiv. iodobenzene, 0.05 equiv. palladium acetate, 0.1 equiv. PPh_3, reflux, 1 day; e) 1.2 equiv. NaH, THF, 1.2 equiv. alkyl halide, 0 °C, 5 h.

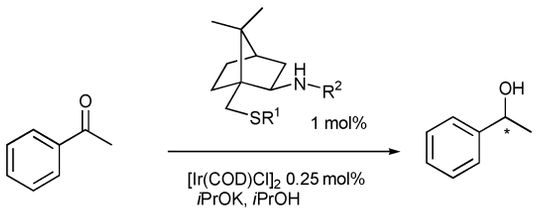


Scheme 3 Synthesis of the ligands. (a) $NaBH_4$ 10 equiv., $NiCl_2$ 2 equiv., MeOH; (b) $HCONH_2$ 7 equiv.; (c) $LiAlH_4$ 1 equiv., THF; (d) DIBAL-H 6 equiv., Et_2O; (e) $BnNH_2$ 1 equiv., $BF_3{\cdot}OEt_2$ 0.15 equiv., benzene.

acetophenone in isopropanol using this iridium complex and isopropoxide as a base. The results using ligands **6a**–**d** and **7a**–**f** are shown in Table 1 and Table 2, respectively. All reactions were performed using a substrate : catalyst ratio of 200 : 1.

The best results were obtained using ligand **6a** having a primary amine and a methyl group attached to the sulfur (Table 1, entry 1). Full conversion was reached after 0.5 hour and the alcohol was produced in 80% ee. Attempts to improve

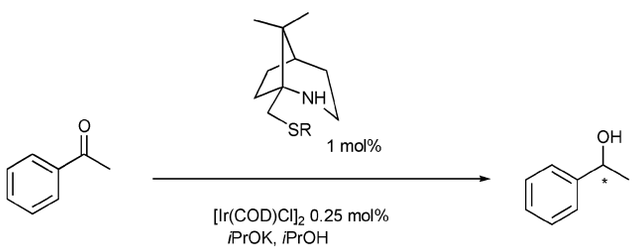
Table 1 Transfer hydrogenation using ligands **6a**–**d** and **8a**[a]



Entry	Ligand	R^1	R^2	Time (h)	Conv. (%)[b]	Ee (%)[b,c]
1	**6a**	Me	H	0.5	100	80
2	**6b**	Et	H	12	74	30
3	**6c**	*i*Pr	H	24	0	—
4	**6d**	Bn	H	12	93	70
5	**8a**	Me	Me	12	100	0

[a] See the Experimental section for procedure. [b] Determined by chiral GC. [c] The major product being the *S* isomer.

Table 2 Transfer hydrogenation using ligands **7a**–**f**[a]



Entry	Ligand	R	Time (h)	Conv. (%)[b]	Ee (%)[b,c]
1	**7a**	Me	1	33	50
			24	89	49
2	**7b**	Et	1	36	43
			24	73	43
3	**7d**	Bn	1	35	26
			24	93	26
4	**7e**	Ph	1	24	0
			24	65	0
5	**7f**	H	1	43	60
			24	90	60

[a] See the Experimental section for procedure. [b] Determined by chiral GC. [c] The major product was identified as the *S* isomer.

the selectivity by changing the substituent at the sulfur were unsuccessful. When an ethyl group (**6b**, Table 1, entry 2) was introduced on the sulfur atom, a dramatic decrease in both reactivity and enantioselectivity resulted, giving 74% conversion and 30% ee after 12 hours. Replacement of the methyl by a benzyl group (**6d**, Table 1, entry 4) resulted in a less dramatic decrease of activity and selectivity (93% conversion after 12 h and 70% ee). Introduction of the more bulky isopropyl group (Table 1, entry 3) resulted in complete loss of reactivity. No conversion was observed after 24 hours. The unreactivity of ligand **6c** is probably caused by the excessive bulk of the isopropyl group which prevents metal–ligand complex formation. Next we decided to tune the amine functionality and see if it would affect the activity or the selectivity of the catalyst. Using ligand **8a** (Table 1, entry 5) full conversion was reached after 12 hours but unfortunately a racemic product was obtained. According to these results the primary amine seems necessary in order to get any discrimination between the two prochiral faces of the acetophenone.

We later tried to increase the selectivity of the catalyst by reducing the size of the chelate from a 6- to a 5-membered ring by moving the nitrogen atom into the bicyclic ring in order to create a more rigid chelate. The 1,2 aminothiol ligand was tested in the transfer hydrogenation of acetophenone using the same reaction conditions as described earlier. However, this class of ligand resulted in a poor catalyst activity; for ligands **7a**–**f**, 24 hours were necessary to reach 90% conversion in all cases compared to ligand **6a**, which required only 0.5 hour to reach full conversion. We could also notice a decrease in the selectivity compared to the 1,3-aminothiol, leading to modest enantiomeric excess. The best result was obtained using the free thiol **7f**, which gave 90% conversion and 60% ee after 24 hours. Once again a close relationship exists between the bulkiness of the substituent on the sulfur atom and the enantiopurity of the product. The enantioselectivity of the reaction decreases with respect to the bulkiness of the alkyl substituent and leads to a racemic alcohol when a phenyl group is used. We can also see a noticeable dependence between the catalyst reactivity and the sulfur substituent but to a lower extent than the 1,3 series.

Ligand **9a** containing a tertiary nitrogen atom was also synthesised and tested in the transfer hydrogenation. As expected, no conversion was observed after 24 hours, suggesting that at least one H atom should be present on the amino group of the ligand in order to form an active catalyst with the iridium salt.

Conclusion

Two series of sulfur- and nitrogen-containing ligands involving 6- and 5-membered chelating rings with iridium(I) metal were synthesised and evaluated in the asymmetric transfer hydrogenation of acetophenone. Ligand **6a** gave rise to a catalyst of good selectivity and activity, 80% ee and full conversion after 30 minutes. A short 5-step synthetic route leading to both series of ligands has been developed using the chiral pool as the source of chirality. The most successful series of ligands was the 1,3 aminothiol giving a 6-membered chelate with the metal. Higher selectivity and activity were observed despite the large freedom of this system compared to the 1,2 aminothiol ligands that offer a more rigid 5-membered chelate. These results suggest that the formation of the catalyst and/or its reactivity are very dependent on the bulkiness of the ligand substitution on the nitrogen and sulfur atoms.

Experimental

General

All reactions were performed under argon or nitrogen using dry glassware and magnetic stirring. THF and Et_2O were freshly distilled under nitrogen from a deep-blue solution of sodium–benzophenone just prior to use. CH_2Cl_2 and *i*PrOH were freshly distilled under nitrogen from powdered CaH_2 just prior to use. Flash chromatography was performed using Matrex silica gel 60 Å (37–70 μm). Analytical TLC was carried out utilising 0.25 mm precoated plates from Merck, silica gel 60 UV_{254} and spots were visualised by the use of UV light and ethanolic phosphomolybdic acid followed by heating. ^1H and ^{13}C NMR spectra were recorded on a Varian 300 or a Varian Unity 400 spectrometer at ambient temperature for $CDCl_3$ solutions. Chemical shifts for protons are reported using the residual $CHCl_3$ as internal reference (δ 7.26). Carbon signals are referred to the shift from the ^{13}C signal of $CDCl_3$ (δ 77.0). Infrared spectra were recorded on a Perkin-Elmer 1760 FT-IR spectrometer. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. Mass spectra were recorded using a Finnigan MAT GCQ PLUS system (EI; 70 eV) or a Varian Saturn 2100T GC/MS (EI). GC analysis was performed using a Varian 3400 instrument equipped with a CP-Chirasil-Dex CB column with N_2 as carrier gas at 15 psi and an FID detector.

(1*S*)-(+)-Camphorsulfonyl chloride (2). According to a literature procedure[14] (1*S*)-(+)-10-camphorsulfonic acid **1** (20.0 g, 79.9 mmol) was added portion-wise to thionyl chloride

(20.4 ml, 280 mmol, 3.5 equiv.), and stirring for 10 min at room temperature was followed by heating at reflux for 2 hours. The unreacted thionyl chloride was distilled and the last traces were removed by azeotropic distillation with toluene (2 × 30 ml) to yield a white solid (21.0 g, 98%). All spectroscopic and physical data were in agreement with those published.[14]

(1*S*,4*R*)-10-Mercaptomethyl-7,7-dimethyl-bicyclo[2.2.1]-heptan-2-one (3). According to a literature procedure[15] (1*S*)-(+)-camphorsulfonyl chloride **2** (18.8 g, 75.0 mmol) and triphenylphosphine (59.0 g, 225 mmol, 3 equiv.) were refluxed in a mixture of water (50 ml) and 1,4-dioxane (200 ml) for 2 hours. After cooling of the reaction mixture, the solution was extracted with pentane (300 ml and 3 × 150 ml). The combined organic phases were washed with water (2 × 150 ml), brine (100 ml), dried over $MgSO_4$ and filtered. After evaporation of the solvent, the resulting solid was purified by flash chromatography (pentane–AcOEt 98 : 2) to give thiol **3** (12.1 g, 65.7 mmol, 88%) as a white crystalline solid. All spectroscopic and physical data were in agreement with those published.[15]

General procedure for the alkylation of thiols 4a–e[16]

(1*S*,4*R*)-7,7-Dimethyl-1-methylsulfanylmethyl-bicyclo[2.2.1]-heptan-2-one (4a). To a solution of thiol **3** (4.00 g, 21.7 mmol) in THF (150 ml), at 0 °C, was added NaH (60%, 1.04 g, 26.0 mmol, 1.2 equiv.) and then methyl iodide (1.62 ml, 26.0 mmol, 1.2 equiv.). After 5 hours, the excess of NaH was decomposed with ethanol and water. The solution was extracted with CH_2Cl_2 (3 × 100 ml), dried over $MgSO_4$ and filtered. The solvent was evaporated and the residue was purified by flash chromatography (pentane–EtOAc 90 : 10) to yield **4a** (3.91 g, 19.7 mmol, 91%) as a colourless oil. All spectroscopic and physical data were in agreement with those published.[17]

(1*S*,4*R*)-1-Ethylsulfanylmethyl-7,7-dimethyl-bicyclo[2.2.1]-heptan-2-one (4b). Following the general procedure, compound **3** (1.5 g, 8.14 mmol) and ethyl iodide (0.782 ml, 9.77 mmol) afforded after purification by flash chromatography (pentane–AcOEt 95 : 5) 1.55 g of **4b** (7.3 mmol, 90%) as a colourless oil. $[\alpha]^{23}_D$ +30.5 (*c* 1.44, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 3H), 1.05 (s, 3H), 1.19–1.32 (t, *J* = 7.6 Hz, 3H), 1.31–1.41 (m, 1H), 1.45–1.53 (m, 1H), 1.83–1.89, (d, *J* = 12.8 Hz, 1H), 1.98–2.17 (m, 3H), 2.33–2.39 (m, 1H), 2.52–2.60 (m, 3H), 2.79–2.84 (d, *J* = 12.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9, 20.4, 20.5, 26.9, 27.1, 28.6, 29.1, 43.4, 43.7, 48.0, 61.1, 219.1; MS (EI) *m*/*z* (rel. intensity) 213 (M^+, 100), 183 (33); HRMS (FAB^+) calculated for $C_{12}H_{20}OS$: 212.1235; found: 213.1307 $[M+H]^+$.

(1*S*,4*R*)-1-Isopropylsulfanylmethyl-7,7-dimethyl-bicyclo-[2.2.1]heptan-2-one (4c). Following the general procedure, thiol **3** (1.93 g, 10.5 mmol) and isopropyl bromide (1.18 ml, 12.6 mmol) afforded after purification by flash chromatography (pentane–AcOEt 95 : 5) 2.01 g (8.88 mmol, 85%) of **4c** as a colourless oil. R_f 0.57 (pentane–AcOEt 90 : 10); $[\alpha]^{23}_D$ +30.5 (*c* 1.18, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (s, 3H), 1.06 (s, 3H), 1.27 (d, *J* = 6.8 Hz, 3H), 1.28 (d, *J* = 6.7 Hz, 3H), 1.30–1.52 (m, 2H), 1.82–2.18 (4H), 2.30–2.43 (m, 1H), 2.55 (d, *J* = 12.9 Hz, 1H), 2.82 (d, *J* = 12.9 Hz, 1H), 2.84–2.95 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 20.4, 23.2, 26.5, 26.9, 27.3, 36.9, 43.1, 43.4, 47.8, 60.7, 206.9. MS (EI) *m*/*z* (rel. intensity) 226 (M^+, 88), 183 (82), 165 (30), 150 (30), 127 (22), 113 (31), 81 (43); HRMS (FAB^+) calculated for $C_{13}H_{22}OS$: 226.1391; found: 227.1467 $[M+H]^+$.

(1*S*,4*R*)-1-Benzylsulfanylmethyl-7,7-dimethyl-bicyclo[2.2.1]-heptan-2-one (4d). Following the general procedure, thiol **3** (2.01 g, 10.9 mmol) and benzyl bromide (1.30 ml, 13.1 mmol) afforded after purification by flash chromatography (pentane–AcOEt 95 : 5) 2.41 g (8.72 mmol, 80%) of **4d** as a colourless oil. R_f 0.54 (pentane–AcOEt 90 : 10); $[\alpha]^{23}_D$ +49.4 (*c* 1.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (s, 3H), 0.98 (s, 3H), 1.18–1.49 (m, 2H), 1.79–2.05 (4H), 2.26–2.40 (m, 1H), 2.43 (d, *J* = 12.9 Hz, 1H), 2.75 (d, *J* = 12.9 Hz, 1H), 3.75 (s, 2H), 7.18–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 26.7, 26.9, 28.3, 38.5, 43.1, 43.5, 47.8, 60.9, 126.9, 128.4, 129.0, 138.4. MS (EI) *m*/*z* (rel. intensity) 274 (M^+, 78), 183 (100), 182 (25), 165 (15), 107 (15), 91 (22); HRMS (FAB^+) calculated for $C_{17}H_{22}OS$: 274.1391; found: 275.1460 $[M+H]^+$.

(1*S*,4*R*)-1-Phenylsulfanylmethyl-7,7-dimethyl-bicyclo[2.2.1]-heptan-2-one (4e). A solution of sodium ethoxide was prepared by stirring a mixture of ethanol (150 ml) and sodium (1 g, 43 mmol) for 30 min under nitrogen. Thiol **3** (4 g, 21.7 mmol), iodobenzene (2.66 ml, 24 mmol), palladium acetate (242 g, 1.1 mmol) and triphenylphosphine (586 mg, 2.2 mmol) were added to the solution. After refluxing the solution for 24 hours with stirring, ethanol was driven off with a rotary evaporator. From the residue the product was extracted into pentane. After washing with water, the organic phase was dried over $MgSO_4$ and filtered. The solvent was evaporated and the residue was purified by flash chromatography (pentane–EtOAc 90 : 10) to afford 4.1 g (15.7 mmol, 72%) of **4e** as a colourless oil. $[\alpha]^{23}_D$ −3.2 (*c* 1.01, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 3H), 1.11 (s, 3H), 1.37–1.44 (m, 1H), 1.51–1.59 (m, 1H), 1.89–1.94 (d, *J* = 18.2, 1H), 1.96–2.18 (m, 3H), 2.38–2.46 (m, 1H), 2.92–2.98 (d, *J* = 12.8, 1H), 2.22–3.36 (d, *J* = 12.8, 1H), 7.10–7.19 (m, 1H), 7.25–7.39 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.44, 20.61, 26.80, 27.16, 31.14, 43.35, 44.69, 48.17, 61.10, 125.90, 128.87, 129.10, 137.72, 217.40. MS (EI) *m*/*z* (rel. intensity) 260 (M^+, 100), 204 (35), 151 (25), 109 (30); HRMS (FAB^+) calculated for $C_{16}H_{20}OS$: 260.1235; found: 261.1308 $[M+H]^+$.

General procedure for the formation of oximes 5a–f[18]

(1*S*,4*R*)-1-Methylsulfanylmethyl-7,7-dimethyl-bicyclo[2.2.1]-heptan-2-one oxime (5a). A solution of **4a** (1.00 g, 5.04 mmol), pyridine (1.22 ml, 15.1 mmol, 3 equiv.) and NH_2OH-HCl (1.75 g, 25.2 mmol, 5 equiv.) in 96% ethanol (25 ml) was stirred under reflux overnight. The ethanol was evaporated and a solution of 10% HCl (20 ml) was added to the residue. The mixture was extracted with CH_2Cl_2 (3 × 40 ml), washed with brine (20 ml), dried over $MgSO_4$, and filtered. After evaporation of the solvent, the oxime was purified by flash chromatography (pentane–AcOEt 85 : 15) and 1.01 g (4.73 mmol, 94%) of **5a** was obtained as a white solid. R_f 0.38 (pentane–EtOAc 85 : 15); $[\alpha]^{23}_D$ −73.1 (*c* 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (s, 3H), 1.00 (s, 3H), 1.22–1.35 (m, 1H), 1.60–1.71 (m, 1H), 1.81–2.13 (4H), 2.15 (s, 3H), 2.50–2.65 (m, 1H), 2.57 (d, *J* = 12.2 Hz, 1H), 2.88 (d, *J* = 12.2 Hz, 1H), 8.30–8.70 (br. s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 19.1, 19.4, 26.8, 29.3, 32.6, 33.6, 43.7, 49.2, 54.7, 167.9. MS (EI) *m*/*z* (rel. intensity) 213 (M^+, 14), 196 (100), 107 (10), 91 (14); HRMS (FAB^+) calculated for $C_{11}H_{19}NOS$: 213.1187; found: 214.1165 $[M+H]^+$.

(1*S*,4*R*)-1-Ethylsulfanylmethyl-7,7-dimethyl-bicyclo[2.2.1]-heptan-2-one oxime (5b). Following the general procedure, ketone **4b** (1.5 g, 7.06 mmol) furnished after purification by flash chromatography (pentane–AcOEt 90 : 10) 1.60 g (6.49 mmol, 92%) of **5b** as a white solid. $[\alpha]^{23}_D$ −61.5 (*c* 0.885, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (s, 3H), 0.99 (s, 3H), 1.22–1.32 (m, 4H), 1.61–1.68 (m, 1H), 1.81–2.01 (m, 3H), 2.02–2.09 (d, *J* = 12.9 Hz, 1H), 2.51–2.63 (m, 4H), 2.85–2.91 (d, *J* = 12.9 Hz, 1H), 8.31 (br. s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 19.8, 20.0, 27.3, 28.6, 30.0, 31.2, 33.2, 44.3, 49.8, 55.1, 168.6; MS (EI) *m*/*z* (rel. intensity) 228 ($[M+H]^+$, 90), 210 (100); HRMS (FAB^+) calculated for $C_{12}H_{21}NOS$: 241.1500; found: 242.1568 $[M+H]^+$.

(1*S*,4*R*)-1-Isopropylsulfanylmethyl-7,7-dimethyl-bicyclo-[2.2.1]heptan-2-one oxime (5c). Following the general procedure, ketone **4c** (500 mg, 2.21 mmol) furnished after purification by flash chromatography (pentane–AcOEt 90 : 10) 481 mg (2.00 mmol, 90%) of **5c** as a white solid. R_f 0.52 (pentane–AcOEt 85 : 15); $[\alpha]^{23}_D$ −55.6 (*c* 0.65, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (s, 3H), 1.00 (s, 3H), 1.27 (d, *J* = 6.6 Hz, 3H), 1.28 (d, *J* = 6.6 Hz, 3H), 1.57–1.68 (m, 1H), 1.78–2.10 (m, 4H), 2.51–2.60 (m, 1H), 2.59 (d, *J* = 12.0 Hz, 1H), 2.78–2.91 (m, 1H), 2.87 (d, *J* = 12.0 Hz, 1H), 8.1 (br. s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 19.8, 23.3, 27.1, 29.4, 29.7, 32.9, 36.9, 44.1, 49.5, 54.7, 77.2, 168.6; MS (EI) *m*/*z* (rel. intensity) 241 (M^+, 15), 224 (100), 198 (20), 182 (30), 167 (32), 150 (25), 126 (14); HRMS (FAB^+) calculated for $C_{13}H_{23}NOS$: 227.1344; found: 228.1443 $[M+H]^+$.

(1*S*,4*R*)-1-Benzylsulfanylmethyl-7,7-dimethyl-bicyclo[2.2.1]-heptan-2-one oxime (5d). Following the general procedure, ketone **4d** (500 mg, 1.81 mmol) furnished after purification by flash chromatography (pentane–AcOEt 95 : 5) 464 mg (1.59 mmol, 88%) of **5d** as a colourless oil. R_f 0.40 (pentane–AcOEt 85 : 15); $[\alpha]^{23}_D$ −24.6 (*c* 0.41, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (s, 3H), 0.89 (s, 3H), 1.15–1.30 (m, 1H), 1.52–1.70 (m, 1H), 1.71–1.90 (m, 3H), 2.03–2.12 (m, 1H), 2.50 (d, *J* = 12.2 Hz, 1H), 2.52–2.63 (m, 1H), 2.82 (d, *J* = 12.2 Hz, 1H), 3.73 (d, *J* = 3.4 Hz, 2H), 7.16–7.38 (m, 5H), 8.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 19.7, 27.0, 29.7, 30.4, 32.9, 38.5, 44.1, 49.5, 54.8, 126.9, 128.3, 129.1, 138.4, 168.2; MS (EI) *m*/*z* (rel. intensity) 289 (M^+, 3), 198 (100), 150.1 (8), 91 (19); HRMS (FAB^+) calculated for $C_{17}H_{23}NOS$: 289.1500; found: 290.1548 $[M+H]^+$.

(1*S*,4*R*)-1-Phenylsulfanylmethyl-7,7-dimethyl-bicyclo[2.2.1]-heptan-2-one oxime (5e). Following the general procedure, ketone **4e** (2 g, 7.68 mmol) furnished after purification by flash chromatography (pentane–AcOEt 95 : 5) 1.87 g (6.84 mmol, 89%) of **5e** as a white solid. $[\alpha]^{23}_D$ −75.6 (*c* 1.15, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 3H), 1.04 (s, 3H), 1.25–1.36 (m, 1H), 1.69–1.77 (m, 1H), 1.85–2.05 (m, 3H), 1.06–1.13 (d, *J* = 17.6 Hz, 1H), 2.57–2.66 (m, 1H), 2.98–3.04 (d, *J* = 12 Hz, 1H), 2.33–2.39 (d, *J* = 12 Hz, 1H), 7.14–7-19 (m, 1H), 7.25–7.31 (m, 2H), 7.35–7.45 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 20.0, 27.4, 30.0, 33.1, 33.3, 44.4, 49.9, 55.2, 125.8 (2C), 123.0 (3C), 139.5, 168.8; MS (EI) *m*/*z* (rel. intensity) 276 (M^+, 50), 258 (100); HRMS (FAB^+) calculated for $C_{16}H_{21}NOS$: 275.1344; found: 276.1462 $[M+H]^+$.

(1*S*,4*R*)-1-Mercaptomethyl-7,7-dimethyl-bicyclo[2.2.1]-heptan-2-one oxime (5f). Following the general procedure, ketone **3** (2 g, 10.80 mmol) furnished after purification by flash chromatography (pentane–AcOEt 90 : 10) 2.02 g (10.15 mmol, 94%) of **5f** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (s, 3H), 0.97 (s, 3H), 1.22–1.34 (m, 1H), 1.75–1.98 (m, 6H), 2.01–2.09 (d, *J* = 17.6 Hz, 1H), 2.42–2.50 (m, 1H), 2.53–2.62 (m, 1H), 2.85–2.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.78, 20.01, 27.35, 28.69, 30.02, 31.20, 33.12, 44.41, 49.72, 167.56; HRMS (FAB^+) calculated for $C_{10}H_{17}NOS$: 199.1031; found: 200.1112 $[M+H]^+$.

General procedure for the reduction of oxime with $NaBH_4$–$NiCl_2$ [19]

(1*S*,2*R*,4*R*)-1-Methylsulfanylmethyl-7,7-dimethyl-bicyclo-[2.2.1]heptan-2-ylamine (6a). To a solution of the oxime **5a** (1.00 g, 4.69 mmol) and $NiCl_2$ (1.21 g, 9.83 mmol, 2 equiv.) in methanol (60 ml), at −30 °C, $NaBH_4$ (1.77 g, 46.9 mmol, 10 equiv.) was added in portions over 1 hour. The reaction mixture was further stirred for 1 hour at −30 °C, and 2 hours at room temperature. After evaporation of the solvent, a 3 M NaOH solution (8 ml) was added followed by ether (50 ml) and the suspension was filtered. The phases were separated and the organic phase was washed with brine (2 × 10 ml), dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (CH_2Cl_2–MeOH 98 : 2) to yield **6a** (541 mg, 2.71 mmol, 58%) as a colourless oil. R_f 0.36 (CH_2Cl_2–MeOH 90 : 10); $[\alpha]^{23}_D$ −76.0 (*c* 0.81, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (s, 3H), 1.03 (s, 3H), 1.04–1.17 (m, 1H), 1.21–1.32 (m, 1H), 1.39–1.62 (m, 4H), 1.63–1.79 (m, 3H), 2.15 (s, 3H), 2.50 (d, *J* = 11.1 Hz, 1H), 2.78 (d, *J* = 11.1 Hz, 1H), 2.95–3.03 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2, 20.1, 21.1, 27.1, 33.3, 35.0, 39.7, 45.2, 47.9, 51.6, 57.7; MS (EI) *m*/*z* (rel. intensity) 200 ($[M+1]^+$ 100), 183 (24), 152 (25); HRMS (FAB^+) calculated for $C_{11}H_{21}NS$: 199.1395; found: 200.1475 $[M+H]^+$.

(1*S*,2*R*,4*R*)-1-Ethylsulfanylmethyl-7,7-dimethyl-bicyclo-[2.2.1]heptan-2-ylamine (6b). Following the general procedure, oxime **5b** (533 mg, 2.34 mmol) gave after purification by flash chromatography (CH_2Cl_2–MeOH–Et_3N 95 : 4 : 1) 294 mg (1.38 mmol, 59%) of **6b** as a colourless oil. $[\alpha]^{23}_D$ −84.6 (*c* 1.15, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (s, 3H), 1.06 (s, 3H), 1.25–1.34 (m, 6H), 1.55–1.62 (m, 3H), 1.69–1.79 (m, 3H), 2.42–2.63 (m, 3H), 2.78–2.83 (d, *J* = 8.9, 1H), 3.00–3.05 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9, 20.4, 21.4, 27.4, 27.6, 32.1, 33.6, 39.9, 44.4, 45.5, 48.1, 57.9; MS (EI) *m*/*z* (rel. intensity) 214 ($[M+1]^+$ 100), 183 (17), 152 (22); HRMS (FAB^+) calculated for $C_{12}H_{23}NS$: 213.1551; found 214.1646 $[M+H]^+$.

(1*S*,2*R*,4*R*)-1-Isopropylsulfanylmethyl-7,7-dimethyl-bicyclo-[2.2.1]heptan-2-ylamine (6c). Following the general procedure, oxime **5c** (354 mg, 1.46 mmol) gave after purification by flash chromatography (CH_2Cl_2–MeOH–Et_3N 95 : 4 : 1) 201 mg (0.88 mmol, 61%) of **6c** as a colourless oil. $[\alpha]^{23}_D$ −57.4 (*c* 0.81, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 3H), 1.04 (s, 3H), 1.04–1.17 (m, 1H), 1.19–1.32 (m, 1H), 1.29 (d, *J* = 6.7 Hz, 3H), 1.30 (d, *J* = 6.7 Hz, 3H), 1.47–1.62 (4H), 1.63–1.79 (3H), 2.52 (d, *J* = 10.7 Hz, 1H), 2.77 (d, *J* = 10.7 Hz, 1H), 2.82–2.92 (m, 1H), 2.93–3.02 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 21.1, 23.5, 27.1, 30.2, 33.3, 36.0, 39.5, 45.2, 47.9, 51.0, 57.5. MS (EI) *m*/*z* (rel. intensity) 228 ($[M+1]^+$ 100), 152 (50), 107 (33); HRMS (FAB^+) calculated for $C_{13}H_{25}NS$: 227.1708; found: 228.1809 $[M+H]^+$.

(1*S*,2*R*,4*R*)-1-Benzylsulfanylmethyl-7,7-dimethyl-bicyclo-[2.2.1]heptan-2-ylamine (6d). Following the general procedure, oxime **5d** (351 mg, 1.20 mmol) furnished after purification by flash chromatography (CH_2Cl_2–MeOH–Et_3N 95 : 4 : 1) 170 mg (0.61 mmol, 51%) of **6d** as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.803 (s, 3H), 0.972 (s, 3H), 1.02–1.11 (m, 2H), 1.17–1.34 (m, 2H), 1.45–1.57 (m, 2H), 1.63–1.79 (m, 3H), 2.45–2.51 (d, *J* = 11.2 Hz, 1H), 2.64–2.70 (d, *J* = 11.2 Hz, 1H), 7.22–7.27 (m, 1H), 7.29–7.39 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 21.4, 27.3, 31.8, 33.5, 38.0, 39.9, 45.4, 48.1, 51.5, 57.9, 127.2, 128.7, 129.0; MS (EI) *m*/*z* (rel. intensity) 276 ($[M+1]^+$ 100), 184 (46), 152 (40), 91 (41); calculated for $C_{17}H_{25}NS$: 275.1708; found: 276.1788 $[M+H]^+$.

(1*S*,2*R*,4*R*)-1-Methylsulfanylmethyl-7,7-dimethyl-bicyclo-[2.2.1]heptan-2-ylmethylamine 8a [20]. A solution of **6a** (181 mg, 0.91 mmol) and formamide (250 µl, 12.8 mmol, 7 equiv.) was heated at 120 °C for 15 min, then poured on water (2 ml) and extracted with CH_2Cl_2 (3 × 20 ml) to yield 197 mg (0.87 mmol, 96%) of a colourless oil. This crude product was dissolved in THF (5 ml) and added to a suspension of $LiAlH_4$ (33 mg, 0.87 mmol) in THF (5 ml). The mixture was refluxed overnight and cooled. 33 µl of H_2O, 33 µl of a 15% NaOH solution and 100 µl of H_2O were sequentially added, the resulting suspension was filtered and the solution was washed with ether. After evaporation of the solvents, the residue was purified by flash chromatography (CH_2Cl_2–MeOH–Et_3N 92 : 7 : 1) to afford 164 mg (0.77 mmol, 88%) of **8a** as a colourless oil. $[\alpha]^{23}_D$ −109.1 (*c* 0.83,

$CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (s, 3H), 1.03 (s, 3H), 1.29–1.40 (m, 1H), 1.48–1.80 (m, 7H), 2.13 (s, 3H), 2.30 (s, 3H), 2.50 (d, J = 11.4 Hz, 1H), 2.62–2.78 (m, 1H), 2.73 (d, J = 11.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2, 20.4, 20.8, 27.2, 34.0, 34.4, 34.8, 36.8, 45.4, 47.9, 51.7, 66.2; MS (EI) *m*/*z* (rel. intensity) 214 (M^+, 38), 166 (100), 152 (48), 135 (54); HRMS (FAB$^+$) calculated for $C_{12}H_{23}NS$: 213.1551; found: 214.1611 $[M+H]^+$.

General procedure for the rearrangement of oxime with DIBAL[21]

(1*S*,5*R*)-8,8-Dimethyl-1-methylsulfanylmethyl-2-aza-bicyclo-[3.2.1]octane (7a). DIBAL 1.5 M in hexane (6.46 ml, 9.70 mmol, 6 equiv.) was added to a solution of the oxime **5a** (345 mg, 1.62 mmol) in Et_2O (14 ml) at room temperature. After 36 hours under reflux, the reaction mixture was cooled to 0 °C and a solution of 10% NaOH (5 ml) was added. The aqueous phase was extracted with Et_2O (3 × 15 ml), dried over Na_2SO_4 and filtered. The residue was purified by flash chromatography (CH_2Cl_2–MeOH 98 : 2) to yield **7a** (158 mg, 0.83 mmol, 49%) as a colourless oil. $[\alpha]^{23}_D$ −68.3 (*c* 0.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (s, 3H), 1.00 (s, 3H), 1.01–1.11 (m, 1H), 1.12–1.28 (m, 3H), 1.40–1.72 (m, 5H), 2.11 (s, 3H), 2.46 (d, J = 11.0 Hz, 1H), 2.74 (d, J = 11.2 Hz, 1H), 2.88–3.00 (br. s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2, 20.2, 21.1, 27.1, 33.3, 34.9, 45.2, 47.9, 57.6; MS (EI) *m*/*z* (rel. intensity) 200 ($[M+H]^+$, 100), 152 (98), 135 (51), 107 (50); HRMS (FAB$^+$) calculated for $C_{11}H_{21}NS$: 199.1395; found: 200.1487 $[M+H]^+$.

(1*S*,5*R*)-8,8-Dimethyl-1-ethylsulfanylmethyl-2-aza-bicyclo-[3.2.1]octane (7b). Following the general procedure, oxime **5b** (400 mg, 1.76 mmol) furnished after purification by flash chromatography (CH_2Cl_2–MeOH 98 : 2) 192 mg (51%) of **7b** as a colourless oil. $[\alpha]^{23}_D$ −86.8 (*c* 1.36, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (s, 3H), 1.04, (s, 3H), 1.23–1.32 (m, 5H), 1.49–1.63 (m, 4H), 1.66–1.78 (m, 3H), 2.51–2.61 (m, 3H), 2.75–2.81 (d, J = 12 Hz, 1H), 2.96–3.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.47, 19,78, 20.75, 22.27, 26.73, 27.07, 29.27, 31.49, 33.96, 39.29, 44.90, 57.40. MS (EI) *m*/*z* (rel. intensity) 214 ($[M+H]^+$, 100), 197 (12), 152 (19); HRMS (FAB$^+$) calculated for $C_{12}H_{23}NS$: 213.1551; found: 214.1623 $[M+H]^+$.

(1*S*,5*R*)-8,8-Dimethyl-1-benzylsulfanylmethyl-2-aza-bicyclo-[3.2.1]octane (7d). Following the general procedure, oxime **5d** (500 mg, 1.81 mmol) furnished after purification by flash chromatography (CH_2Cl_2–MeOH 98 : 2) 238 mg (48%) of **7d** as a colourless oil. $[\alpha]^{23}_D$ −61.9 (*c* 1.02, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (s, 3H), 0.97 (s, 3H), 1.03–1.14 (m, 1H), 1.18–1.32 (m, 3H), 1.46–1.57 (m, 2H), 1.63–1.76 (m, 3H), 2.48 (d, J = 11.2 Hz, 1H), 2.67 (d, J = 11.2 Hz, 1H), 3.66–3.79 (m, 2H), 7.22–7.28 (m, 1H), 4.29–7.38 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 21.4, 27.4, 31.8, 33.5, 38.0, 39.9, 45.4, 48.1, 51.5, 57.9, 127.2, 128.7 (2C), 129.0 (2C), 134.1; (EI) *m*/*z* (rel. intensity) 276 ($[M+H]^+$, 100), 184 (54), 152 (56), 91 (77); HRMS (FAB$^+$) calculated for $C_{17}H_{25}NS$: 275.1708; found: 276.1792 $[M+H]^+$.

(1*S*,5*R*)-8,8-Dimethyl-1-phenylsulfanylmethyl-2-aza-bicyclo-[3.2.1]octane (7e). Following the general procedure, oxime **5e** (400 mg, 1.44 mmol) furnished after purification by flash chromatography (CH_2Cl_2–MeOH 98 : 2) 170 mg (0.65 mmol, 45%) of **7e** as a colourless oil. $[\alpha]^{23}_D$ −37.2 (*c* 1.03, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 3H), 0.96–1.01 (d, J = 10.2 Hz, 1H), 1.12 (s, 3H), 1.40–1.65 (m, 3H), 1.76–2.02 (m, 4H), 2.89–3.05 (m, 3H), 3.12–3.18 (d, J = 12 Hz, 1H), 7.10–7.19 (m, 1H), 7.21–7.38 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 25.4, 26.8, 28.5, 29.0, 30.3, 34.9, 39.8, 41.7, 46.0, 126.4, 128.2, 129.4 (2C), 129.9 (2C); MS (EI) *m*/*z* (rel. intensity) 262 ($[M+H]^+$, 100), 152 (94); HRMS (FAB$^+$) calculated for $C_{16}H_{23}NS$: 261.1551; found: 262.1626 $[M+H]^+$.

(1*S*,5*R*)-(8,8-Dimethyl-2-aza-bicyclo[3.2.1]oct-1-yl)-methanethiol (7f). Following the general procedure, oxime **5f** (400 mg, 1.36 mmol) furnished after purification by flash chromatography (CH_2Cl_2–MeOH 98 : 2) 118 mg (0.64 mmol, 47%) of **7f** as a colourless oil. $[\alpha]^{23}_D$ −184.0 (*c* 0.661, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (s, 1H), 1.07 (s, 1H), 1.10–1.21 (m, 2H), 1.27–1.42 (m, 3H), 1.54–1.66 (m, 2H), 1.69–1.82 (m, 3H), 2.85–2.89 (d, J = 9.6 Hz, 1H), 3.03–3.07 (m, 1H), 3.17–3.21 (d, J = 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 21.4, 27.3, 33.3, 40.3, 40.9, 45.6, 46.5, 48.6, 57.6; MS (EI) *m*/*z* (rel. intensity) 185 (M^+, 100), 107 (35); HRMS (FAB$^+$) calculated for $C_{10}H_{19}NS$: 185.1238; found: 186.1318 $[M+H]^+$.

Benzyl[(1*S*,4*R*)-7,7-dimethyl-1-methylsulfanylmethyl-bicyclo-[2.2.1]hept-2-ylidene]-amine (9a). Sulfide **4a** (300 mg, 1.51 mmol), benzylamine (165 µl, 1.51 mmol), $BF_3{\cdot}OEt_2$ (3.0 µl, 24 µmol) and dry benzene (10 ml) were refluxed for one day in a Dean–Stark trap. The solution was cooled, washed with brine (2 ml), dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (pentane–AcOEt 92 : 8) to afford 326 mg (1.13 mmol, 75%) of **9a** as a colourless oil. R_f 0.33 (pentane–AcOEt 90 : 10); $[\alpha]^{23}_D$ −26.3 (*c* 0.38, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 3H), 1.08 (s, 3H), 1.20–1.33 (m, 1H), 1.43–1.55 (m, 1H), 1.86–2.00 (3H), 2.16 (s, 3H), 2.35–2.48 (m, 1H), 2.67 (d, J = 13.0 Hz, 1H), 3.06 (d, J = 13.0 Hz, 1H), 4.48 (d, J = 3.9 Hz, 1H), 7.15–7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.4, 20.0, 20.4, 27.3, 28.7, 34.0, 35.5, 44.4, 48.1, 55.5, 57.1, 126.3, 127.3, 128.2, 140.4, 181.7; MS (EI) *m*/*z* (rel. intensity) 288 ($[M+H]^+$, 63), 287 (39), 272 (56), 91 (100); HRMS (FAB$^+$) calculated for $C_{18}H_{25}NS$: 287.1708; found: 288.1770 $[M+H]^+$.

General procedure for transfer hydrogenation of acetophenone with isopropanol as hydrogen source

To a dry 50 ml Schlenk flask under argon was added $[Ir(COD)Cl]_2$ (0.00335 g, 0.005 mmol), ligand (0.025 mmol) and *i*-PrOH (2 ml). The solution was stirred for 30 min at 80 °C and then cooled to rt. *i*-PrOH (18 ml) was added, followed by acetophenone (235 µl, 2.0 mmol) and *i*-PrOK (63 µl, 0.063 mmol, 1.0 M solution in *i*-PrOH). The solution was stirred at room temperature and the enantiomeric excess was determined by chiral GC analysis after various reaction times.

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