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# Synthesis of optically active functionalised cyclic ketimines and their application in enantioselective catalysis

Nikolai Graf v. Keyserlingk and Jürgen Martens*

*Universität Oldenburg, Fachbereich Chemie, Carl-von-Ossietzky-Straße 9-11, D-26129 Oldenburg, Germany*

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**Abstract**—The synthesis of enantiomerically pure cyclic ketimines attached to moieties containing additional donor atoms is described. The resulting optically active chelating ligands are tested in the rhodium-catalysed enantioselective hydrosilylation of acetophenone with respect to their inductive potential. 

## 1. Introduction

Transition metal-catalysed enantioselective reactions have become a versatile tool in organic synthesis[1] and for this reason in recent years many optically active chelating ligands have been synthesised as catalysts for such reactions. Great interest has been drawn towards nitrogen containing compounds due to their availability from the chiral pool and their good properties in the complexation of transition metals.[2] Of special importance have been unsaturated nitrogen-containing compounds such as oxazolines[3] and acyclic imines[4] attached to different functionalised side chains. The use of cyclic five-membered imines in enantioselective catalysis, which would combine the main structural features of both acyclic imines and cyclic 2-oxazolines, has not been described to date.

Thus, we wish to report herein the synthesis of cyclic differently functionalised ketimines and their application in the rhodium-catalysed hydrosilylation of acetophenone as an enantioselective catalytic model reaction.

## 2. Results and discussion

For our investigations into the synthesis of cyclic ketimines we needed a synthetic pathway which would allow a broad variance both of the substituents attached to the imino group and the structure of the cyclic backbone. As a promising synthetic sequence we chose the nucleophilic ring-opening of *N*-Boc-protected lactams by suitable organometallic reagents and ring-closure of the resulting amino ketones after deprotection.

As the starting material for the synthesis of ketimines with a bicyclic backbone, *N*-Boc-lactam **1** was used, which was derived in three steps from the unnatural amino acid (all-*R*)-azabicyclo[3.3.0]octane-2-carboxylic acid.[5] This synthesis has been already described by us elsewhere.[6] Reaction with 2-pyridyllithium or 6-bromo-2-pyridyllithium gave the *N*-Boc-protected amino ketones **2**[6] and **3**. These compounds could not be isolated as analytically pure materials and so were used without characterisation in the next step. Deprotection by treatment with trifluoroacetic acid furnished, after alkaline work-up, the cyclic ketimines **4**[6] and **5** (Scheme 1).

In order to synthesise 6-substituted pyridines, the bromine in the pyridine ring of ketimine **5** was substituted by suitable reagents. Reaction of **5** with phenylboronic acid in the presence of sodium carbonate and a catalytic amount of tetrakis(triphenylphosphine)-palladium(0)[7] afforded, after chromatographic work-up, the 6-phenyl substituted pyridine ketimine **6** as a colourless solid in 90% yield. The coupling of two molecules of **5** was achieved by the use of a Ni(0)–triphenylphosphine complex, which was prepared in situ by reduction of $NiCl_2$ with Zn in the presence of triphenylphosphine.[8] The $C_2$-symmetric tetradentate ligand **7** was isolated in 46% yield as a yellow solid after column chromatography. The tetrakis(triphenylphosphine)palladium(0)-mediated substitution of bro-

* Corresponding author. E-mail: juergen.martens@uni-oldenburg.de

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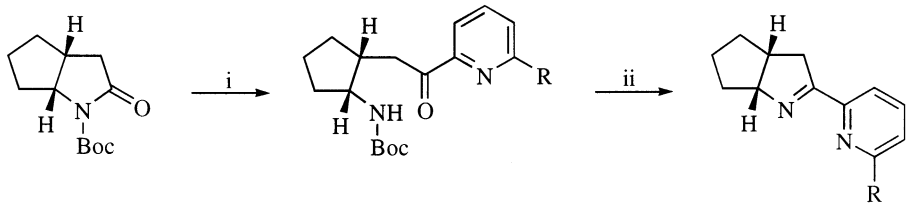



(all-*R*)-**1** (all-*R*)-**2** (R = H), (all-*R*)-**3** (R = Br) (all-*R*)-**4** (R = H), (all-*R*)-**5** (R = Br)

**Scheme 1.** Synthesis of bicyclic pyridine ketimines: (i) 2-pyridyllithium or 6-bromo-2-pyridyllithium, −78°C, 4 h; (ii) 1. trifluoroacetic acid, $CH_2Cl_2$, room temperature, 2. NaOH.

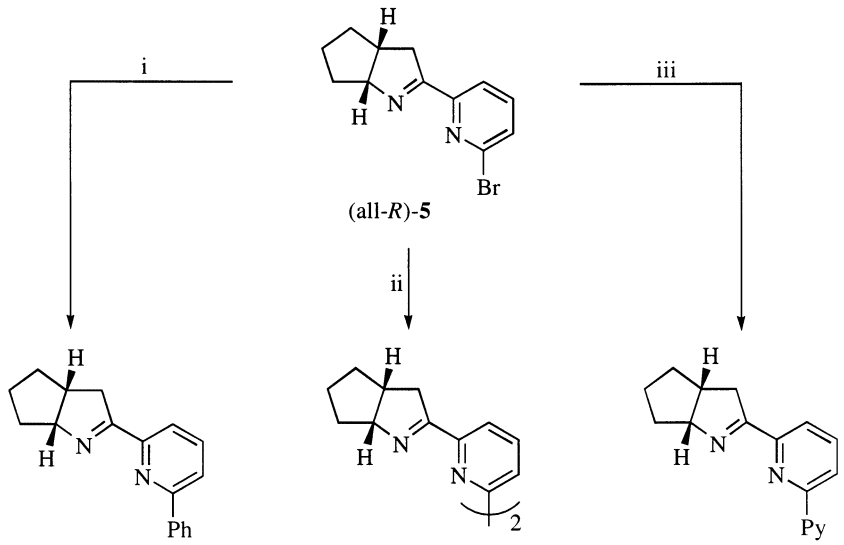
mide by 2-Zn-pyridine[9] was employed in order to prepare the optically active bipyridine derivative **8** in 54% isolated yield (Scheme 2).

In the synthesis of a set of ligands with a monocyclic backbone, compounds derived from (*S*)-pyroglutamic acid **9** were used as the starting materials. The structural variation was achieved by modification of the carboxylic acid group of **9**. The known *N*-Boc-protected 5-methyl-lactam **12**[10] and 5-benzyl compound **14**[11] were synthesised according to literature procedures. The phenylthioether derivative **15** was prepared by nucleophilic substitution of the hydroxyl group of (*S*)-pyroglutaminol **10** with diphenyldisulfide in the presence of tributylphosphine. The sulfur compound **15** was isolated with one equivalent of tributylphosphineoxide. After protection with $Boc_2O$, the *N*-Boc thioether derivative **16** was isolated as analytically pure compound (Scheme 3).

Reaction with 2-pyridyllithium, as described above furnished the *N*-Boc-amino ketones **17**, **18** and **19** and subsequent deprotection gave the ketimines **20**, **21** and **22** (Scheme 4).

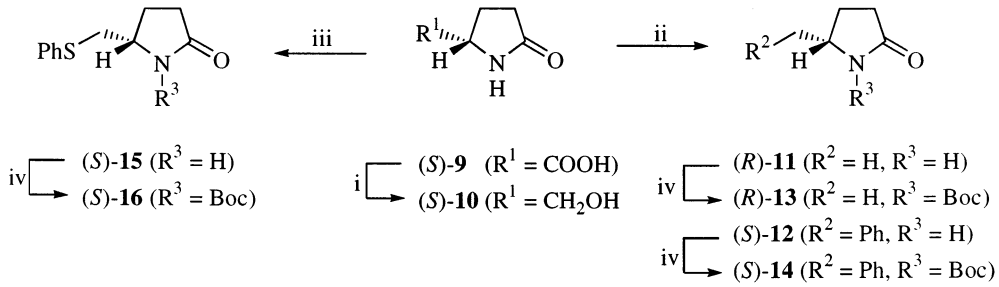
We next investigated the substitution of the pyridine ring in the ketimine **4** by other heteroaromatic and aromatic rings. All three nucleophiles we chose (thiophene, *N*-methylpyrrole and thiophenol) were directly lithiated with *n*-butyllithium according to literature procedures.[12] Reaction with lactam **1** at −78°C, as described above, gave after chromatographic work-up the amino ketones **23**, **24**, and **25** followed by treatment with trifluoroacetic acid, which furnished the hetaryl-substituted ketimines **26**, **27** and **28**. In the case of the methylthioether derivative **25**, dimethylsulphate was added to the reaction mixture at −78°C after addition of the nucleophile in order to methylate in situ the thiolate anion (Scheme 5).

With these ketimines in hand we studied their properties as ligands in enantioselective catalysis. We chose the Rh(I)-catalysed enantioselective hydrosilylation of acetophenone as a model reaction for our investigation.

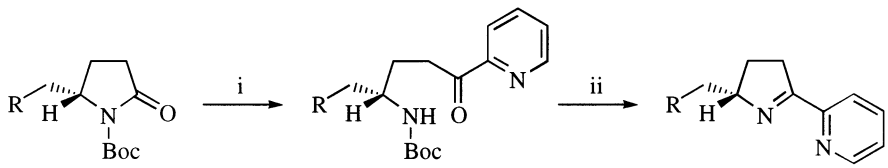



(all-*R*)-**6** (all-*R*)-**5** (all-*R*)-**7** (all-*R*)-**8**

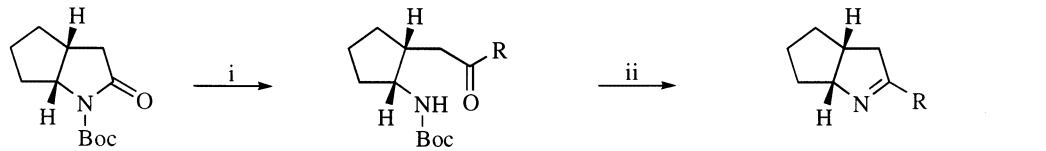
**Scheme 2.** Synthesis of 6-substituted bicyclic pyridine ketimines: (i) phenylboronic acid, $(PPh_3)_4Pd$, $Na_2CO_3$, toluene/MeOH/$H_2O$, 85°C, 6 h; (ii) $NiCl_2$, $PPh_3$, Zn, DMF, 50°C, 4 h; (iii) 2-pyridylzink, $(PPh_3)_4Pd$, THF, room temperature, 16 h; Py = 2-pyridyl.




**Scheme 3.** Synthesis of 5-substituted monocyclic Boc-protected lactams: (i) 1. MeOH, $SOCl_2$; 2. $NaBH_4$, EtOH, Ref. 10; (ii) $R^2=H$, Ref. 10; $R^2=Ph$, Ref. 11; (iii) $Ph_2S_2$, $PBu_3$, pyridine, room temperature 48 h; (iv) $Boc_2O$, DMAP, TEA, $CH_2Cl_2$, room temperature, 12 h.




**Scheme 4.** Synthesis of monocyclic pyridine ketimines: (i) 2-pyridyllithium, −78°C, 4 h; (ii) 1. trifluoroacetic acid, $CH_2Cl_2$, room temperature, 2. NaOH.



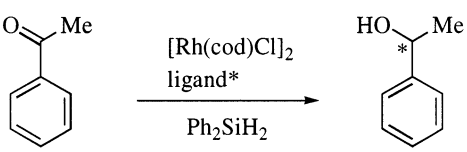

**Scheme 5.** Synthesis of hetaryl- and aryl-substituted ketimines: (i) R = 2-thienyl, 2-*N*-methylpyrrolyl: R-Li, −78°C, 4 h; R = 2-methylsulfanylphenyl: 1. R-Li, −78°C, 4 h; 2. $Me_2SO_4$, −78°C.

### 2.1. Enantioselective hydrosilylation of acetophenone

The enantioselective hydrosilylation of carbonyl compounds provides a good method for the preparation of optically active alcohols.[13] The results of Brunner, who introduced nitrogen containing ligands as catalysts in this reaction, prompted us to test our new ligands in this enantioselective reduction (Scheme 6).[4]

Normally we carried out the reactions without additional solvent at room temperature, using only diphenylsilane and acetophenone as the reaction medium. In some experiments, toluene, diethyl ether or tetrahydrofuran were used as co-solvent. The results are listed in Table 1.

Normally the (*S*)-configured 1-phenylethanol product predominated in reactions catalysed by the ketimine ligands. The opposite direction of chiral induction was observed only in the case of the ligands **5** (R = Br) and **6** (R = Ph), which contain a non-chelating substituent in the 6-position of the pyridine-ring (entries 6 and 7). A similar observation was made by Brunner with a 6-methyl-substituted pyridine-oxazoline as ligand.[14] An additional chelating substituent in the pyridine moiety as was realised in the terdentate ligand **8** (R = Py) and in the tetradentate $C_2$-symmetric pyridylketimine **7**, gave the same direction of induction but lower enantioselectivities than those achieved with the unsubstituted basic structure **4** (entries 8 and 9). Probably in these cases a preferred coordination of the rhodium by the achiral pyridine moieties results in a greater distance between the chiral ligand backbone and the reaction centre.




**Scheme 6.** Enantioselective hydrosilylation of acetophenone.

**Table 1.** Enantioselective hydrosilylation of acetophenone with diphenylsilane

| Entry | Ligand[a] | Solvent | Yield (%) | E.e.[c] (%) | Config.[d] |
|---|---|---|---|---|---|
| 1 | **4**[b] | None | 56 | 10 | *S* |
| 2 | **4** | None | 53 | 28 | *S* |
| 3 | **4** | $Et_2O$ | 39 | 6 | *S* |
| 4 | **4** | THF | 33 | 14 | *S* |
| 5 | **4** | Toluene | 38 | 40 | *S* |
| 6 | **5** | None | 89 | 15 | *R* |
| 7 | **6** | None | 47 | 15 | *R* |
| 8 | **7** | None | 71 | 7 | *S* |
| 9 | **8** | None | 56 | 1 | *S* |
| 10 | **20** | None | 86 | 54 | *S* |
| 11 | **20** | Toluene | 32 | 25 | *S* |
| 12 | **21** | None | 60 | 39 | *S* |
| 13 | **21** | Toluene | 40 | 38 | *S* |
| 14 | **22** | None | 36 | 31 | *S* |
| 15 | **22** | Toluene | 44 | 41 | *S* |
| 16 | **26** | None | 63 | 5 | *R* |
| 17 | **27** | None | 75 | 0 | – |
| 18 | **28** | None | 68 | 26 | *S* |

[a] Ratio rhodium:ligand 1:20.
[b] Ratio rhodium:ligand 1:5.
[c] Determined by GC.
[d] Determined by polarimetry.

Lowering the ligand excess with respect to rhodium from 20 to 5 gave strongly reduced selectivity with almost no change in the yield of the reaction (entry 1, pyridylketimine **4**). A strong influence was observed using an additional solvent as reaction medium. In the case of coordinating solvents such as diethyl ether or tetrahydrofuran, both yields and selectivities were reduced with ligand **4** (entries 3 and 4). Employing toluene as solvent furnished optically active 1-phenylethanol with slightly higher enantioselectivity but lower yields with pyridylketimine **4** (entry 5). The 5-methyl-substituted pyridylketimine **20** gave (*S*)-phenylethanol without any additional solvent in 54% e.e. and 86% chemical yield; here the addition of toluene reduced both the selectivity and the chemical yield (entries 10 and 11). The other monocyclic pyridylimines **21** and **22** were not so much affected by the influence of toluene as co-solvent (especially the thioether derivative **22**, which gave better results with respect to chemical yield and enantioselectivity in the presence of toluene, entry 15), but the enantioselectivity of the hydrosilylation obtained with these two ligands were somewhat lower then those obtained with the 5-methyl derivative **20**. Obviously, the additional donor atom in the thioether pyridylketimine **20** had no influence on the direction of chiral induction in the hydrosilylation reaction.

Substitution of the pyridine ring by other heteroaromatic rings resulted in active ligands with respect to the chemical yields, but with only low chiral induction with the thienylimine **26** or no induction in the case of the *N*-methylpyrrole derivative **27**. Only the 2-methylsulfanylphenyl-substituted ligand **28** gave slightly better results (with 26% e.e.) similar to that obtained with the pyridylketimine **4** (entries 16, 17 and 18).

## 3. Conclusion

A broad range of optically active functionalised cyclic ketimines were synthesised in a two- or three-step procedure from four differently substituted bicyclic and monocyclic *N*-Boc-protected lactams. The reaction sequence first involved addition of an appropriate organolithium reagent to the lactam and subsequent deprotection and intramolecular imine formation. The flexibility of this synthetic sequence is demonstrated by the variation both of chiral backbone and the second donor atom and the neighbourhood of the second donor atom. The obtained cyclic ketimines were then tested as ligands in the Rh(I)-catalysed hydrosilylation of acetophenone and furnished optically active 1-phenylethanol in moderate to good chemical yields with e.e.s of up to 54%.

## 4. Experimental

**General remarks**: Experiments involving organometallic reagents were carried out in oven dried, evacuated glassware under a positive pressure of dry argon. THF and $Et_2O$ were distilled from sodium-benzophenone ketyl. Dichloromethane was distilled from calcium chloride. Analytical thin layer chromatography (TLC) was performed using Merck silica gel 60 $F_{254}$ aluminium sheets. TLC spots were detected with UV light and iodine. Column chromatography was performed using silica gel 60 (particle size 0.040–0.063 mm) from Merck. Gas chromatography (GC) was performed using a Shimadzu (GC-15-A) instrument, 25 m column with the following specifications: SGE Cydex-B (chiral), $\omega_i = 0.25$ mm, film thickness 0.25 μm, 1 μL product in *n*-hexane, FID detection, nitrogen carrier gas. Melting points (uncorrected) were determined in open capil-

laries using an apparatus according to Dr. Lindström. Infrared spectra were recorded using a Beckman IR 4220 spectrometer as KBr discs for solids and as films between NaCl plates for liquids. The $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AM 300 or a Bruker ARX 500 spectrometer. The chemical shifts are reported in the $\delta$ scale (ppm) relative to residual non-deuterated solvent or tetramethylsilane (TMS) in $CDCl_3$ as solvent. Coupling constants, $J$, are given in hertz (Hz). Optical rotations were measured with a Perkin–Elmer polarimeter 241 MC and mass spectra were measured with a Finnigan-MAT 212 (datasystem SS 300) spectrometer. Elemental analyses were performed with a C, H, N, S Analyser EA 1108 from Fisons Instruments.

The ligands were synthesised using either general procedure 1 or 2.

### 4.1. General procedure 1

Under an atmosphere of dry argon *n*-butyllithium (19.3 mL 1.6 M solution in *n*-hexane, 30.9 mmol) was charged into a dry 250 mL three-necked, round bottomed flask, equipped with a thermometer, a dropping funnel and a septum. The reaction flask was cooled down to −78°C at which temperature a solution of 2-bromopyridine or 2,6-dibromopyridine (27.5 mmol) in anhydrous $Et_2O$ (in the case of 2,6-dibromopyridine a 6:4 (v/v) mixture $Et_2O$/THF was used) (50 mL) was added slowly. After complete addition, the reaction mixture was stirred at −78°C for an additional 30 min. To the dark-red or bright yellow solution the *N*-protected lactam (all-*R*)-**1**, (*R*)-**12**, (*S*)-**14** or (*S*)-**16** (25 mmol), dissolved in anhydrous $Et_2O$ (25 mL), were added dropwise over a period of 15 min. The reaction mixture was stirred for a further 4 h and then slowly warmed to room temperature over 12 h. At this temperature the reaction was hydrolysed with a saturated $NH_4Cl$ solution (40 mL). The cooling bath was removed and the reaction flask was allowed to warm to room temperature. The phases were separated and the aqueous layer was extracted with $Et_2O$ (3×30 mL). The combined organic layers were washed with brine (30 mL) and dried ($MgSO_4$). Evaporation of the solvent gave the crude γ-amino ketones as dark-red oils, which were normally subjected to column chromatography.

### 4.2. General procedure 2

The Boc-protected γ-amino ketone (11.5 mmol) was dissolved in anhydrous $CH_2Cl_2$ (50 mL) and cooled to 0°C. At this temperature trifluoroacetic acid (44 mL) was added dropwise over a period of 30 min. After complete addition the cooling bath was removed and the reaction mixture was allowed to reach room temperature. Stirring was continued for 3 h. The reaction mixture was cooled again to 0°C and NaOH (35% aqueous solution, 70 mL) was added dropwise. During the addition the temperature should not exceed 10°C. The alkaline solution was extracted with $Et_2O$ (3×50 mL) and the combined organic extracts were washed with brine. After drying ($MgSO_4$) the solvent was removed in vacuo. The resulting brown oil was purified by column chromatography.

### 4.3. (all-*R*)-(*N*-*tert*-Butyloxycarbonyl)-2′-aminocyclopent-1-yl-(6-bromopyridin-2-yl)-ethanone (all-*R*)-3

Synthesised using general procedure 1 from *N*-Boc-lactam (all-*R*)-**1**[6] (5.62 g, 25 mmol); the crude product is directly used in the next step; yield: 9.32 g (97%) yellow solid.

### 4.4. (all-*R*)-3-(6-Bromopyridin-2-yl)-azabicyclo[3.3.0]-oct-2-en (all-*R*)-5

Synthesised using general procedure 2 from *N*-Boc-amino ketone (all-*R*)-**3** (9.32 g, 24.40 mmol); column chromatography with ethyl acetate:*n*-hexane:triethylamine 4:1:0.01, $R_f$ value 0.45; yield: 4.95 g (77%) yellow oil which solidified on standing; mp 43–45°C; $[\alpha]_D^{20}=+38.3$ ($c=1.00$, $CH_2Cl_2$); IR (KBr): $\nu$ ($cm^{-1}$)= 2950 ($CH_2$), 1630 (C=N), 1570, 1540 (C-H), 1040 (C-Br); $^1$H NMR ($CDCl_3$): $\delta$ (ppm)=1.32–1.81 (6H, m, 2×H6, 2×H7, 2×H8), 2.81 (1H, m, H5), 2.91 (1H, dd, $J$ 18.7 and $J$ 6.0, H4), 3.30 (1H, dd, $J$ 18.7 and 10.0, H3), 4.82 (1H, m, H1), 7.49 (1H, d, $J$ 7.6, pyridyl-H), 7.57 (1H, t, $J$ 7.7, pyridyl-H), 8.06 (1H, d, $J$ 7.6, pyridyl-H); $^{13}$C NMR ($CDCl_3$): $\delta$ (ppm)=24.07, 33.07, 34.70 (C6, C7, C8), 38.88 (C5), 43.79 (C4), 120.66, 128.81, 138.42 (pyridyl-C), 141.25, 154.38 (q.-pyridyl-C); MS (CI, *i*-butane): $m/z$ (%)=265 (100), 267 (97) [$MH^+$]. Anal. calcd for $C_{12}H_{13}BrN_2$ (264.0): C, 54.36; H, 4.94; N, 10.57. Found: C, 54.12; H, 4.91; N, 10.31%.

### 4.5. (all-*R*)-3-(6-Phenylpyridin-2-yl)-azabicyclo[3.3.0]-oct-2-en (all-*R*)-6

Under an atmosphere of dry argon a three-necked round bottomed 100 mL flask was charged with 6-bromopyridine (1.32 g, 5 mmol) (all-*R*)-**5** and tetrakis(triphenylphosphine)palladium(0) (0.17 g, 0.15 mmol) in toluene (12 mL). Subsequently, sodium carbonate (1.06 g, 10 mmol) in water (6 mL) and phenylboronic acid (0.73 g, 6 mmol) were added. The reaction mixture was stirred for 6 h at 85°C. After cooling to room temperature 25% ammonia solution (3 mL) in saturated sodium carbonate solution (30 mL) was added and the aqueous solution was extracted with $CH_2Cl_2$ (3×50 mL). After washing the combined organic extracts with brine the organic layer was dried ($MgSO_4$). The solvent was evaporated and the solid brown residue was subjected to column chromatography with *n*-hexane:ethyl acetate, 2:1, $R_f$ value=0.43; yield: 1.18 g (90%), colourless solid; mp 82–83°C; $[\alpha]_D^{20}=+160.2$ ($c=1.00$, $CH_2Cl_2$); IR (KBr): $\nu$ ($cm^{-1}$)= 3100 (C-H); 2940, 2850 ($CH_2$); 1600 (C=N); 1550, 820, 765, 695 (C-H); $^1$H NMR ($CDCl_3$): $\delta$ (ppm)=1.43, 1.55, 1.78, 1.93 (6H, 4m, 2×H6, 2×H7, 2×H8), 2.97 (1H, m, H5), 3.08 (1H, dd, $J$ 18.7 and $J$ 2.7, H4), 3.44 (1H, dd, $J$ 18.7 and $J$ 9.9, H4), 4.84 (1H, m, H1), 7.41, 7.46 (3H, 2m, arom-H), 7.75 (2H, m, arom-H), 8.06 (3H, m, arom-H); $^{13}$C NMR ($CDCl_3$): $\delta$ (ppm)=24.16, 33.22, 34.82 (C6, C7, C8), 38.83 (C4), 43.97 (C5), 80.21 (C1), 120.10, 120.71 (pyridyl-C), 126.78, 128.67, 129.01

(arom-C), 136.88 (pyridyl-C), 138.98 (q.-arom-C), 153.14, 156.19 (q.-pyridyl-C), 173.86 (C3); MS (CI, *i*-butane): $m/z$ (%) = 263 (100) [$MH^+$]. Anal. calcd for $C_{18}H_{18}N_2$ (262.2): C, 82.41; H, 6.92; N, 10.68. Found: C, 82.35; H, 6.91; N, 10.57%.

### 4.6. (all-*R*)-6,6′-Bis-(azabicyclo[3.3.0]oct-2-en-3-yl-[2,2′]bipyridine (all-*R*)-7

Under an atmosphere of dry argon a three-necked round bottomed 100 mL flask was charged with $NiCl_2 \cdot 6H_2O$ (2.13 g, 8.98 mmol) and triphenylphosphine (9.40 g, 35.92 mmol) in anhydrous DMF (45 mL). At 50°C Zn-dust (0.58 g, 8.92 mmol) was added in one portion. The mixture was stirred for 1 h at 50°C and then 2.37 g (8.98 mmol) of 6-bromopyridine (all-*R*)-**5** in anhydrous DMF (3 mL) was added dropwise. The reaction mixture was stirred for a further 3.5 h at constant temperature. For work-up the reaction mixture was diluted with a half-concentrated ammonia solution (150 mL) after cooling to room temperature and then extracted with chloroform (3×100 mL). The combined organic extracts were washed with water (3×50 mL) and dried ($MgSO_4$). The solvent was evaporated in vacuo and the oily residue was subjected to column chromatography with *n*-hexane:ethyl acetate:triethylamine 1:1:0.01, $R_f$ value 0.38; yield: 0.77 g (46%), yellow crystalline solid; mp 158–159°C; $[\alpha]_D^{20}$ = +169.6 ($c$ = 1.00, $CH_2Cl_2$); IR (KBr): $\nu$ ($cm^{-1}$) = 2950 ($CH_2$), 1600 (C=N), 1540 (C-H); $^1H$ NMR ($CDCl_3$): $\delta$ (ppm) = 1.32–2.01 (12H, m, 2×H6, 2×H6′, 2×H7, 2×H7′, 2×H8, 2×H8′), 2.83 (2H, m, H5, H5′), 3.08 (2H, dd, $J$ 18.7 and $J$ 6.0, H4, H4′), 3.45 (2H, dd, $J$ 18.7 and $J$ 10.0, H4, H4′), 4.88 (2H, m, H1, H1′), 7.83 (2H, t, $J$ 7.1, pyridyl-H, pyridyl-H′), 8.11 (2H, d, $J$ 7.6, pyridyl-H, pyridyl-H′), 8.51 (2H, d, $J$ 7.6, pyridyl-H, pyridyl-H′); $^{13}C$ NMR ($CDCl_3$): $\delta$ (ppm) = 24.09, 33.13, 34.77 (C6, C6′, C7, C7′, C8, C8′), 38.76 (C5, C5′), 43.88 (C4, C4′), 80.18 (C1, C1′), 121.45, 121.74, 136.92 (6×pyridyl-C), 152.57, 154.88 (2×q.-pyridyl-C), 173.52 (C3, C3′); MS (CI, *i*-butane): $m/z$ (%) = 371 (100) [$MH^+$]. Anal. calcd for $C_{24}H_{26}N_4$ (370.2): C, 77.80; H, 7.07; N, 15.12. Found: C, 77.69; H, 7.01; N, 15.02%.

### 4.7. (all-*R*)-(Azabicyclo[3.3.0]oct-2-en-3-yl-2,2-bipyridine (all-*R*)-8

2-Bromopyridine (1.10 g, 7 mmol) was lithiated in anhydrous THF (20 mL) according to general procedure 1. The resulting organolithium was then quickly transferred at −78°C via syringe into a mixture of $ZnCl_2$ (0.96 g, 7 mmol) in anhydrous THF (20 mL). After the addition was complete the solution was allowed to warm to room temperature and was stirred for 30 min. The clear red solution was again transferred at room temperature via syringe to a flask which was charged with 0.92 g (3.5 mmol) 6-bromopyridine (all-*R*)-**5** and tetrakis(triphenylphosphine)palladium(0) (0.40 g, 0.40 mmol) in anhydrous THF (20 mL). The reaction mixture was stirred for 16 h and then hydrolysed by addition of saturated sodium hydrogen carbonate solution (100 mL). The phases were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3×50 mL). After washing the combined organic extracts with brine (50 mL) and drying ($MgSO_4$) the solvent was evaporated in vacuo. The remaining yellow viscous oil was purified by column chromatography with *n*-hexane:triethylamine 8:2, $R_f$ value 0.36; yield: 0.50 g (54%), yellow viscous oil which slowly crystallised on standing; mp 44–45°C; $[\alpha]_D^{20}$ = +127.4 ($c$ = 1.34, $CH_2Cl_2$); IR (KBr): $\nu$ ($cm^{-1}$) = 2950 ($CH_2$), 1650, 1600 (C=N), 1560 (C-H); $^1H$ NMR ($CDCl_3$): $\delta$ (ppm) = 1.31–2.01 (6H, m, 2×H6, 2×H7, 2×H8), 2.82 (1H, m, H5), 3.09 (1H, dd, $J$ 18.6 and $J$ 3.3, H4), 3.43 (1H, dd, $J$ 18.6 and $J$ 9.9, H4); 4.84 (1H, m, H1), 7.28, 7.82, 8.13, 8.47 (7H, m, pyridyl-H); $^{13}C$ NMR ($CDCl_3$): $\delta$ (ppm) = 24.16, 33.20, 34.84 (C6, C7, C8), 38.84 (C4), 43.95 (C5), 80.24 (C1), 121.04, 121.53, 121.77, 123.71, 136.76, 137.10, 149.07 (pyridyl-C), 152.67, 155.17, 155.95 (q.-pyridyl-C), 173.58 (C3); MS (CI, *i*-butane): $m/z$ (%) = 264 (100) [$MH^+$]. Anal. calcd for $C_{17}H_{17}N_3$ (263.1): C, 77.54; H, 6.51; N, 15.96. Found: C, 77.46; H, 6.49; N, 15.81%.

### 4.8. (*S*)-5-Phenylsulfanylmethyl-pyrrolidin-2-one (*S*)-15

Under an atmosphere of dry argon (*S*)-hydroxymethylpyrrolidin-2-one (*S*)-**10**[10] (1.73 g, 15 mmol) and tributylphosphine (4.55 g, 22.5 mmol) were dissolved in anhydrous pyridine (15 mL). At 0°C diphenyldisulfide (4.91 g, 22.5 mmol) was added in small portions. Stirring was continued in the warming ice-bath for 3 h. After that the reaction mixture was stirred at room temperature for a further 48 h. For work-up the clear yellow solution was diluted with ethyl acetate/water 1:1 (v/v) (100 mL). The phases were separated and the organic layer was washed subsequently with 2 M HCl (30 mL), 2 M NaOH (4×30 mL) and brine (50 mL). After drying ($MgSO_4$) the solvent was removed in vacuo. The resulting yellow oil was subjected to column chromatography with ethyl acetate:triethylamine 9:1, $R_f$ value 0.31. The thioether derivative was isolated with one equivalent tributylphosphineoxidee; yield: 2.72 g (44%) yellow oil with one equivalent of tributylphosphineoxidee; $[\alpha]_D^{20}$ = +29.8 ($c$ = 1.00, $CH_2Cl_2$); IR (NaCl): $\nu$ ($cm^{-1}$) = 1715 (C=O); $^1H$ NMR ($CDCl_3$): $\delta$ (ppm) = 0.91 (9H, t, $J$ = 7.2 Hz, $CH_3$, tributylphosphineoxidee), 1.31–1.87 (20H, m, $(CH_2CH_2CH_2)_3$, H4), 1.93 (1H, m, H4), 2.30 (2H, m, 2×H3), 2.92 (1H, dd, $J$ 13.2 and $J$ 8.2, H1′), 3.10 (1H, dd, $J$ 13.2 and $J$ 5.7, H1′), 3.78 (1H, m, H5), 6.50 (1H, s, N-H), 7.18–7.40 (5H, m, arom.-H); $^{13}C$ NMR ($CDCl_3$): $\delta$ (ppm) = 13.52 (3×$CH_3$), 23.65 (d, $J_{C,P}$ 2.8 Hz), 24.26 (d, $J_{C,P}$ 13.8 Hz), 27.02 (d, $J_{C,P}$ 65.03 Hz) (6×$CH_2$), 26.42 (C4), 29.91 (C3), 40.51 (C1′), 53.29 (C5), 126.87, 129.07, 130.38 (arom.-C), 134.55 (q.-arom.-C), 177.53 (C2); MS (CI, *i*-butane): $m/z$ (%) = 208 (100) [$MH^+$]. $C_{11}H_{13}NOS$ (207.9).

### 4.9. (*S*)-(*N*-*tert*-Butyloxycarbonyl)-5-phenylsulfanylmethyl-pyrrolidin-2-one (*S*)-16

(*S*)-**15** (2.72 g, 6.6 mmol) with one equivalent tributylphosphine oxide were dissolved in anhydrous $CH_2Cl_2$ (10 mL) at room temperature. $Boc_2O$ (2.88 g, 13.2 mmol), DMAP (0.81 g, 6.6 mmol) and triethylamine (0.67 g, 6.6 mmol) were added. Stirring was

continued for 24 h. The reaction mixture was diluted with diethyl ether (50 mL) and washed with 10% aqueous citric acid (2×25 mL), saturated sodium hydrogen carbonate (25 mL) and brine (25 mL). The organic layer was dried ($MgSO_4$) and evaporated. The resulting yellow oil was subjected to column chromatography with *n*-hexane:ethyl acetate 1:1, $R_f$ value 0.63; yield: 1.67 g (82%) colourless, viscous oil; $[\alpha]_D^{20} = -38.4$ ($c = 1.56$, $CH_2Cl_2$); IR (NaCl): $\nu$ ($cm^{-1}$) = 1690 (C=O); $^1H$ NMR ($CDCl_3$): $\delta$ (ppm) = 1.46 (9H, s, $C(CH_3)_3$), 2.09 (2H, m, 2×H4), 2.43 (1H, m, H3), 2.65 (1H, m, H3), 2.96 (1H, dd, *J* 13.6 and *J* 9.4, H1′), 3.42 (1H, dd, *J* 13.6 and *J* 2.6, H1′), 4.31 (1H, m, H5), 7.17–7.34 (3H, m, arom.-H), 7.42 (2H, d, *J* 7.5, arom.-H); $^{13}C$ NMR ($CDCl_3$): $\delta$ (ppm) = 21.70 (C3), 27.94 ($C(CH_3)_3$), 31.09 (C4), 37.25 (C1′), 57.05 (C5), 83.14 ($C(CH_3)_3$), 126.73, 129.09, 130.09 (arom.-C), 135.06 (q.-arom.-C), 149.66 (C=O), 173.89 (C2); MS (CI, *i*-butane): *m*/*z* (%) = 208 (100) [$MH^+ - C_4H_8 - CO_2$]. Anal. calcd for $C_{16}H_{21}NO_3S$ (307.4): C, 62.51; H, 6.89; N, 4.56; S, 10.43: Found: C, 62.46; H, 7.01; N, 4.32; S, 10.22%.

### 4.10. (*R*)-(*N*-*tert*-Butyloxycarbonyl)-4-amino-1-pyridin-2-yl-pentan-1-one (*R*)-17

Synthesised using general procedure 1 from *N*-Boc-lactam (*S*)-**12**[10] (4.98 g, 25 mmol); column chromatography with *n*-hexane:ethyl acetate:triethylamine 2:1:0.01, $R_f$ value 0.46; yield: 4.56 g (66%) colourless oil which solidified on standing; mp 63–64°C; $[\alpha]_D^{20} = +0.9$ ($c = 1.10$, $CH_2Cl_2$); IR (KBr): $\nu$ ($cm^{-1}$) = 3350 (N-H), 2950 ($CH_2$), 1650 (C=O), 1550, 1500 (C-H); $^1H$ NMR ($CDCl_3$): $\delta$ (ppm) = 1.19 (3H, d, *J* 6.6, $CH_3$), 1.40 (9H, s, $C(CH_3)_3$), 1.78–1.94 (2H, m, 2×H3), 3.29 (2H, t, *J* 7.1, 2×H2), 3.76 (1H, m, H4), 4.52 (1H, s, N*H*), 7.45 (1H, ddd, *J* 7.7, *J* 4.9 and *J* 1.7, pyridyl-H), 7.82 (1H, dt, *J* 7.7 and *J* 1.7, pyridyl-H), 8.04 (1H, d, *J* 7.7, pyridyl-H), 8.67 (1H, d, *J* 4.9, pyridyl-H); $^{13}C$ NMR ($CDCl_3$): $\delta$ (ppm) = 20.22 ($CH_3$), 28.35 ($C(CH_3)_3$), 31.05 (C3), 34.35 (C2), 46.40 (C4), 78.87 ($C(CH_3)_3$), 121.75, 127.03, 136.82, 148.86 (pyridyl-C), 153.29 (q.-pyridyl-C), 155.38 (C=O), 201.49 (C1); MS (CI, *i*-butane): *m*/*z* (%) = 223 (100) [$MH^+ - C_4H_8$), 279 (20) [$MH^+$]. Anal. calcd for $C_{15}H_{22}N_2O_3$ (278.2): C, 64.73; H, 7.97; N, 10.06. Found: C, 64.78; H, 7.90; N, 10.11%.

### 4.11. (*S*)-(*N*-*tert*-Butyloxycarbonyl)-4-amino-5-phenyl-1-pyridin-2-yl-pentan-1-one (*S*)-18

Synthesised using general procedure 1 from *N*-Boc-lactam (*R*)-**14**[11] (5.00 g, 18.18 mmol); column chromatography with *n*-hexane:ethyl acetate:triethylamine 2:1:0.01, $R_f$ value 0.35; yield: 3.82 g (59%) colourless solid; mp 89–90°C; $[\alpha]_D^{20} = -0.9$ ($c = 0.68$, $CH_2Cl_2$); IR (KBr): $\nu$ ($cm^{-1}$) = 3350 (N-H), 2950 ($CH_3$, $CH_2$), 1680 (C=O), 1520, 770 (C-H); $^1H$ NMR ($CDCl_3$): $\delta$ (ppm) = 1.36 (9H, s, $C(CH_3)_3$), 1.76 (1H, m, H3), 1.96 (1H, m, H3), 2.80 (2H, m, H2, H5); 3.29 (2H, m, H2, H5), 3.93 (1H, m, H4), 4.55 (1H, s, N-*H*), 7.14–7.34 (5H, m, arom-H), 7.45 (1H, t, *J* 4.9, pyridyl-H), 7.81 (1H, t, *J* 7.9, pyridyl-H), 8.01 (1H, d, *J* 7.9, pyridyl-H), 8.65 (1H, d, *J* 4.9, pyridyl-H); $^{13}C$ NMR ($CDCl_3$): $\delta$ (ppm) = 27.98 (C3), 28.27 ($C(CH_3)_3$), 34.36 (C2), 41.53 (C4), 51.56 (C5), 78.93 (($C(CH_3)_3$), 121.73, 126.24, 127.06, 128.28, 129.47, 136.81, 148.82 (arom.-C, pyridyl-C), 138.02, 153.16 (q.-arom-C, q.-pyridyl-C), 155.41 (C=O), 201.50 (C1); MS (CI, *i*-butane): *m*/*z* (%) = 237 (100) [$MH^+ - C_4H_8 - CO_2 - H_2O$]. Anal. calcd for $C_{21}H_{26}NO_3$ (354.4): C, 71.16; H, 7.39; N, 7.90. Found: C, 71.70; H, 7.73; N, 7.94%.

### 4.12. (*S*)-(*N*-*tert*-Butyloxycarbonyl)-4-amino-5-sulfanyl-phenyl-1-pyridin-2-yl-pentan-1-one (*S*)-19

Synthesised using general procedure 1 from *N*-Boc-lactam (*S*)-**16** (3.07 g, 10 mmol); column chromatography with *n*-hexane:ethyl acetate:triethylamine 4:1:0.02, $R_f$ value 0.33; yield: 1.13 g (29%), brown solid; mp 58–60°C; $[\alpha]_D^{20} = +9.5$ ($c = 1.13$, $CH_2Cl_2$); IR (KBr): $\nu$ ($cm^{-1}$) = 3370 (N-H), 2950 ($CH_3$, $CH_2$), 1690 (C=O), 1500, 750 (C-H); $^1H$ NMR ($CDCl_3$): $\delta$ (ppm) = 1.39 (9H, s, $C(CH_3)_3$), 1.91, 2.10 (2H, 2m, 2×H3), 3.18 (4H, m, 2×H2, 2×H5), 3.82 (1H, m, H4), 4.85 (1H, s, N-*H*), 7.12–7.52 (6H, m, arom.-H, pyridyl-H), 7.81 (1H, m, pyridyl-H), 8.05 (1H, t, *J* 7.2, pyridyl-H), 8.66 (1H, d, *J* 4.1, pyridyl-H); $^{13}C$ NMR ($CDCl_3$): $\delta$ (ppm) = 27.83 (C3), 28.29 ($C(CH_3)_3$), 34.25 (C2), 39.38 (C4), 50.31 (C5), 79.27 ($C(CH_3)_3$), 121.79, 127.10, 136.84, 148.87 (pyridyl-C), 126.18, 128.96, 129.62 (arom.-C), 136.36 (q.-arom.-C), 153.20 (q.-pyridyl-C), 155.32 (C=O), 201.18 (C1); MS (CI, *i*-butane): *m*/*z* (%) = 269 (100) [$MH^+ - C_4H_8 - CO_2 - H_2O$]; 387 (30) [$MH^+$]. Anal. calcd for $C_{21}H_{26}N_2O_3S$ (386.2): C, 65.26; H, 6.78; N, 7.25; S, 8.29. Found: C, 65.11; H, 6.81; N, 7.30; S 8.06%.

### 4.13. (*R*)-2-(5-Methyl-4,5-dihydro-3*H*-pyrrol-2-yl-pyridine (*R*)-20

Synthesised using general procedure 2 from (*R*)-**17** (4.42 g, 15.89 mmol); column chromatography with *n*-hexane:ethyl acetate:triethylamine 1:7:0.02, $R_f$ value 0.31; yield 1.55 g (61%) colourless oil; $[\alpha]_D^{20} = +96.8$ ($c = 1.00$, $CH_2Cl_2$); IR (NaCl): $\nu$ ($cm^{-1}$) = 2950 ($CH_2$), 1600 (C=N), 1570, 1550 (C-H); $^1H$ NMR ($CDCl_3$): $\delta$ (ppm) = 1.39 (3H, d, *J* 7.2, $CH_3$), 1.58 (1H, m, H4), 2.26 (1H, m, H4), 3.01 (1H, m, H3), 3.22 (1H, m, H3), 4.35 (1H, m, H5), 7.28 (1H, t, *J* 5.9, pyridyl-H), 7.71 (1H, t, *J* 7.9, pyridyl-H), 8.12 (1H, d, *J* 7.9, pyridyl-H), 8.64 (1H, d, *J* 5.9, pyridyl-H); $^{13}C$ NMR ($CDCl_3$): $\delta$ (ppm) = 21.88 ($CH_3$), 30.44 (C4), 34.96 (C3), 68.94 (C5), 121.90, 124.39, 136.11, 148.94 (pyridyl-C), 153.28 (q.-pyridyl-C), 173.45 (C2); MS (CI, *i*-butane) *m*/*z* (%) = 161 (100) [$MH^+$]. Anal. calcd for $C_{10}H_{12}N_2$ (160.1): C, 74.97; H, 7.55; N, 17.48. Found: C, 74.68; H, 7.51; N, 17.31%.

### 4.14. (*S*)-2-(5-Benzyl-4,5-dihydro-3*H*-pyrrol-2-yl-pyridine (*S*)-21

Synthesised using general procedure 2 from (*S*)-**18** (3.63 g, 10.25 mmol); column chromatography with *n*-hexane:ethyl acetate:triethylamine 4:1:0.02, $R_f$ value 0.23; yield: 2.10 g (87%) slightly yellow viscous oil; $[\alpha]_D^{20} = +31.7$ ($c = 1.00$, $CH_2Cl_2$); IR (NaCl): $\nu$ ($cm^{-1}$) = 2950 ($CH_2$), 1610 (C=N), 1530, 730, 700 (C-H); $^1H$ NMR ($CDCl_3$): $\delta$ (ppm) = 1.71 (1H, m, H4), 2.08 (1H, m, H4),

2.74 (1H, dd, *J* 13.7 and *J* 8.8, H1′), 2.98 (1H, m, H3), 3.08 (1H, m, H3), 3.31 (1H, dd, *J* 13.7 and *J* 5.5, H1′), 4.55 (1H, m, H5), 7.18–7.33 (6H, m, arom.-H, pyridyl-H), 7.74 (1H, dt, *J* 7.7 and *J* 1.6; pyridyl.-H), 8.15 (1H, d, *J* 7.7, pyridyl-H), 8.63 (1H, d, *J* 4.9, pyridyl-H); $^{13}$C NMR ($CDCl_3$): $\delta$ (ppm) = 27.82 (C4), 34.68 (C3), 42.34 (C1′), 74.80 (C5), 122.02, 124.57, 126.07, 128.23, 129.36, 136.23, 149.06 (arom.-C, pyridyl-C), 139.34 (q.-arom.-C), 153.26 (q.-pyridyl-C), 174.29 (C2); MS (CI, *i*-butane): *m*/*z* (%) = 237 (100) [MH$^+$]. Anal. calcd for $C_{16}H_{16}N_2$ (236.1): C, 81.32; H, 6.82; N, 11.85. Found: C, 81.12; H, 6.73; N, 11.81%.

### 4.15. (*S*)-2-(5-Phenylsulfanylmethyl-4,5-dihydro-3*H*-pyrrol-2-yl)-pyridine (*S*)-22

Synthesised using general procedure 2 from crude (*S*)-**19** (8.47 g, 21.94 mmol); column chromatography with *n*-hexane:ethyl acetate:triethylamine 4:1:0.02, $R_f$ value 0.24; yield: 2.60 g (44%) yellow oil which solidified on standing; mp 35–36°C; $[\alpha]_D^{20}$ = +44.1 (*c* = 1.89, $CH_2Cl_2$); IR (KBr): *v* (cm$^{-1}$) = 2920 ($CH_2$), 1610 C=N), 1565, 780, 730, 680 (C-H); $^1$H NMR ($CDCl_3$): $\delta$ (ppm) = 1.85 (1H, m, H4), 2.28 (1H, m, H4), 3.05 (1H, dd, *J* 13.2 and *J* 8.3, H1′), 3.08 (1H, m, H3), 3.24 (1H, m, H3), 3.52 (1H, dd, *J* 13.2 and *J* 4.9, H1′), 4.51 (1H, m, H5), 7.10–7.47 (6H, m, arom.-H, pyridyl-H), 7.70 (1H, dt, *J* 7.9 and *J* 1.9, pyridyl-H), 8.05 (1H, d, *J* 7.9, pyridyl-H), 8.63 (1H, d, *J* 4.1, pyridyl-H); $^{13}$C NMR ($CDCl_3$): $\delta$ (ppm) = 27.87 (C4), 35.11 (C3), 39.66 (C1′), 72.96 (C5), 122.15, 124.68, 136.20, 149.06 (pyridyl-C), 125.89, 128.80, 129.30 (arom.-C), 136.57 (q.-arom.-C), 152.96 (q.-arom.-C), 175.14 (C2); MS (CI, *i*-butane): *m*/*z* (%) = 269 (100) [MH$^+$]. Anal. calcd for $C_{16}H_{16}N_2S$ (268.1): C, 71.61; H, 6.01; N, 10.44; S, 11.95. Found: C, 71.51; H, 5.95; N, 10.33; S, 11.91%.

### 4.16. (all-*R*)-(*N*-*tert*-Butyloxycarbonyl)-2′-aminocyclopent-1′-yl-(2-thienyl)-ethanone (all-*R*)-23

Reaction of 2-thienyllithium (from thiophene (6.05 g, 72 mmol) and *n*-butyllithium (60 mmol) according to Ref. 12) with *N*-Boc-lactam (all-*R*)-**1**[6] (11.25 g, 50 mmol) as described in general procedure 1; column chromatography with *n*-hexane:ethyl acetate:triethylamine 4:1:0.01, $R_f$ value 0.38; yield: 10.04 g (65%) colourless oil which solidified on standing; mp 64°C; $[\alpha]_D^{20}$ = +24.0 (*c* = 1.065, $CH_2Cl_2$); IR (KBr): *v* (cm$^{-1}$) = 3350 (N-H), 2950 ($CH_3$, $CH_2$), 1660 (C2O); $^1$H NMR ($CDCl_3$): $\delta$ (ppm) = 1.22–2.07 (6H, m, 2×H3′, 2×H4′, 2×H5′), 1.41 (9H, s, $C(CH_3)_3$), 2.54 (1H, m, H1′), 2.67 (1H, m, H2), 3.18 (1H, m, H2), 4.09 (1H, m, H2′), 4.52 (1H, s, N-*H*), 7.10 (1H, t, *J* 4.9, thienyl-H), 7.59 (1H, d, *J* 3.1, thienyl-H), 7.69 (1H, d, *J* 4.9, thienyl-H); $^{13}$C NMR ($CDCl_3$): $\delta$ (ppm) = 21.66, 29.14, 31.96 (C3′, C4′, C5′), 39.63 (C1′), 39.65 (C2), 54.29 (C2′), 79.09 ($C(CH_3)_3$), 127.95, 131.73, 133.23 (thienyl-C), 144.50 (q.-thienyl-C), 155.55 (C=O), 192.77 (C1); MS (CI, *i*-butane): *m*/*z* (%) = 253 (100) [MH$^+$–$C_4H_8$), 310 (40) [MH$^+$]. Anal. calcd for $C_{16}H_{23}NO_3S$ (309.1): C, 62.11; H, 7.49; N, 4.53; S, 10.36. Found: C, 62.01; H, 7.60; N, 4.50; S, 10.12%.

### 4.17. (all-*R*)-(*N*-*tert*-Butyloxycarbonyl)-2′-aminocyclopent-1′-yl-(2-*N*-methylpyrrolyl)-ethanone (all-*R*)-24

Reaction of 2-*N*-methylpyrrolyllithium (from *N*-methylpyrrole (0.98 g, 12.1 mmol) and *n*-butyllithium (11 mmol) according to Ref. 12) with *N*-Boc-lactam (all-*R*)-**1**[6] (2.25 g (10 mmol) as described in general procedure 1; column chromatography with *n*-hexane:ethyl acetate:triethylamine 4:1:0.01, $R_f$ value 0.36; yield: 1.56 g (51%) colourless oil which solidified on standing; mp 98°C; $[\alpha]_D^{20}$ = +33.3 (*c* = 1.10, $CH_2Cl_2$); IR (KBr): *v* (cm$^{-1}$) = 3290 (N-H), 2950 ($CH_3$, $CH_2$), 1690 (C=O); $^1$H NMR ($CDCl_3$): $\delta$ (ppm) = 1.17–2.06 (6H, m, 2×H3′, 2×H4′, 2×H5′), 1.42 (9H, s, $C(CH_3)_3$), 2.52 (2H, m, H1, H2′), 3.02 (1H, d, *J* 10.9, H1), 3.93 (3H, s, N-$CH_3$), 4.08 (1H, m, H1′), 4.52 (1H, s, N-*H*), 6.10 (1H, m, pyrrolyl-H), 6.78 (1H, m, pyrrolyl.-H), 6.94 (1H, d, *J* 3.0, pyrrolyl-H); $^{13}$C NMR ($CDCl_3$): $\delta$ (ppm) = 21.60, 29.26, 32.10 (C3′, C4′, C5′), 28.35 ($C(CH_3)_3$), 37.61 (N-$CH_3$), 39.27 (C2′), 39.84 (C1), 54.52 (C1′), 79.15 ($C(CH_3)_3$), 107.77, 119.01, 130.76 (pyrrolyl-C), 130.96 (q.-pyrrolyl-C), 155.58 (C=O), 190.82 (C1); MS (CI, *i*-butane): *m*/*z* (%) = 307 (100) [MH$^+$]. Anal. calcd for $C_{17}H_{26}N_2O_3$ (306.2): C, 66.64; H, 8.55; N, 9.14. Found: C, 66.50; H, 8.61; N, 8.99%.

### 4.18. (all-*R*)-(*N*-*tert*-Butyloxycarbonyl)-2′-aminocyclopent-1′-yl-(2-methylsulfanylphenyl)-ethanone (all-*R*)-25

2-Lithiumphenyllithiumthiolate was generated from thiophenol (1.82 g, 16.5 mmol) and *n*-butyllithium (36 mmol) in anhydrous cyclohexane (25 mL) according to Ref. 12. After adding anhydrous THF (25 mL) at 0°C the solution was cooled to −78°C. At this temperature lactam (all-*R*)-**1**[6] (3.38 g, 15 mmol) in anhydrous THF (20 mL) was added. Stirring was continued for 4 h, then the reaction mixture was allowed to warm up to −40°C and stirred for 1 h at this temperature. The flask was cooled again to −78°C and dimethylsulphate (2.08 g, 16.5 mmol) were added via syringe. Within 12 h the reaction was warmed to room temperature. Work-up was performed according to general procedure 1; column chromatography with *n*-hexane:ethyl acetate:triethylamine 4:1:0.02, $R_f$ value 0.67; yield: 3.10 g (59%) colourless oil; $[\alpha]_D^{20}$ = +4.2 (*c* = 1.15); IR (NaCl): *v* (cm$^{-1}$) = 3300 (N-H), 2950 ($CH_3$, $CH_2$), 1680 (C=O), 750 (C-H); $^1$H NMR ($CDCl_3$): $\delta$ (ppm) = 1.15–2.07 (6H, m, 2×H3′, 2×H4′, 2×H5′), 1.43 (9H, s, $C(CH_3)_3$), 2.42 (3H, s, $SCH_3$), 2.51 (1H, m, H2′), 2.76 (1H, m, H1), 3.30 (1H, d, *J* 15.5, H1), 4.16 (1H, m, H1′), 4.46 (1H, s, N-*H*), 7.15 (1H, t, *J* 7.5, arom.-H), 7.30 (1H, m, arom.-H), 7.47 (1H, m, arom.-H), 7.79 (1H, d, *J* 7.9, arom.-H); $^{13}$C NMR ($CDCl_3$): $\delta$ (ppm) = 16.00 ($SCH_3$), 20.97, 29.22, 32.08 (C3′, C4′, C5′), 28.32 ($C(CH_3)_3$), 39.49 (C2′), 40.57 (C2), 54.43 (C1′), 79.10 ($C(CH_3)_3$), 123.47, 125.20, 130.03, 131.87 (arom.-C), 135.01, 141.93 (q.-arom.-H), 155.60 (C=O), 201.22 (C1); MS (CI, *i*-butane): *m*/*z* = 250 (100) [MH$^+$–$C_4H_8$–$CO_2$]. Anal. calcd for $C_{19}H_{27}NO_3S$ (349.2): C, 65.30; H, 7.79; N, 4.01; S, 9.18. Found: C, 65.08; H, 7.80; N, 4.12; S, 9.15%.

### 4.19. (all-*R*)-3-(Thiophen-2-yl)-azabicyclo[3.3.0]oct-2-en (all-*R*)-26

Synthesised using general procedure 2 from crude amino ketone (all-*R*)-**23** (12.25 g, 39.64 mmol); column chromatography *n*-hexane:ethyl acetate:triethylamine 4:1:0.01, $R_f$ value 0.43; recrystallisation of the resulting brown solid residue from $CH_2Cl_2$/*n*-hexane; yield 6.07 g (80%), colourless crystalline solid; mp 49–50°C; $[\alpha]_D^{20}$ = +9.8 ($c$ = 1.00, $CH_2Cl_2$); IR (KBr): $\nu$ ($cm^{-1}$) = 2950, 2850 ($CH_2$), 1600 (C=N); $^1H$ NMR ($CDCl_3$): $\delta$ (ppm) = 1.32–1.99 (6H, m, 2×H6, 2×H7, 2×H8); 2.69 (1H, d, $J$ 17.3, H4), 2.81 (1H, m, H5), 3.20 (1H, dd, $J$ 17.3, $J$ 9.8, H4), 4.74 (1H, m, H1), 7.04 (1H, t, $J$ 4.9, thienyl-H), 7.28 (1H, d, $J$ 3.0, thienyl-H), 7.37 (1H, d, $J$ 4.9, thienyl-H); $^{13}C$ NMR ($CDCl_3$): $\delta$ (ppm) = 24.18, 33.18, 34.76 (C6, C7, C8), 39.53 (C5), 44.46 (C4), 79.40 (C1), 127.33, 128.78, 128.97 (thienyl-C), 139.47 (q.-thienyl-C), 165.92 (C3); MS (CI, *i*-butane): $m/z$ (%) = 192 (100) [$MH^+$]. Anal. calcd for $C_{11}H_{13}NS$ (191.1): C, 69.07; H, 6.85; N, 7.32; S, 16.76. Found: C, 68.95; H, 6.81; N, 7.43; S, 16.65%.

### 4.20. (all-*R*)-3-(*N*-Methylpyrrol-2-yl)-azabicyclo[3.3.0]-oct-2-en (all-*R*)-27

Synthesised using general procedure 2 from amino ketone (all-*R*)-**24** (2.31 g, 7.53 mmol); column chromatography *n*-hexane:ethyl acetate:triethylamine 4:1:0.01, $R_f$ value 0.64; yield: 0.89 g (63%), colourless oil; $[\alpha]_D^{20}$ = +3.0 ($c$ = 0.50, $CH_2Cl_2$); IR (NaCl): $\nu$ ($cm^{-1}$) = 2940 ($CH_2$, $CH_3$), 1600 (C=N); $^1H$ NMR ($CDCl_3$): $\delta$ (ppm) = 1.25–1.90 (6H, m, 2×H6, 2×H7, 2×H8), 2.65 (2H, m, H4, H5), 3.17 (1H, dd, $J$ 18.1 and $J$ 11.3, H4), 3.97 (3H, s, N-$CH_3$), 4.76 (1H, m, H1), 6.10 (1H, m, pyrrolyl-H), 6.44 (1H, d, $J$ 1.9, pyrrolyl-H), 6.69 (1H, m, pyrrolyl-H); $^{13}C$ NMR ($CDCl_3$): $\delta$ (ppm) = 24.02, 33.81, 34.75 (C6, C7, C8), 37.36 (N-$CH_3$), 38.00 (C5), 45.62 (C4), 79.98 (C1), 107.22, 114.53, 127.27 (pyrrolyl-C); 127.69 (q.-pyrrolyl-C), 164.09 (C3); MS (CI, *i*-butane): $m/z$ (%) = 189 (100) [$MH^+$]. Anal. calcd for $C_{12}H_{16}N_2$ (188.1): C, 76.55; H, 8.57; N, 14.88; Found: C, 76.43; H, 8.45; N, 14.71%.

### 4.21. (all-*R*)-3-(2-Methylsulfanylphenyl)-azabicyclo-[3.3.0]-oct-2-en (all-*R*)-28

Synthesised using general procedure 2 from amino ketone (all-*R*)-**25** (3.10 g, 8.80 mmol); column chromatography *n*-hexane:ethyl acetate:triethylamine 4:1:0.01, $R_f$ value 0.29; yield: 1.74 g (86%) colourless solid; mp 69–70°C; $[\alpha]_D^{20}$ = −14.4 ($c$ = 1.19, $CH_2Cl_2$); IR (KBr): $\nu$ ($cm^{-1}$) = 2915, 2840 ($CH_3$, $CH_2$), 1600 (C=N), 750, 725, 700 (C-H); $^1H$ NMR ($CDCl_3$): $\delta$ (ppm) = 1.39–2.09 (6H, m, 2×H6, 2×H7, 2×H8), 2.41 (3H, s, $SCH_3$), 2.76 (2H, m, H4, H5), 3.25 (1H, dd, $J$ 16.5 and $J$ 8.8, H4), 4.88 (1H, m, H1), 7.10 (1H, dt, $J$ 7.7 and $J$ 1.7, arom.-H), 7.27 (2H, m, arom.-H), 7.39 (1H, dd, $J$ 7.7 and $J$ 1.1, arom.-H); $^{13}C$ NMR ($CDCl_3$): $\delta$ (ppm) = 16.35 ($SCH_3$), 24.03, 33.41, 34.80 (C6, C7, C8), 38.84 (C4), 46.54 (C5), 80.06 (C1), 123.84, 125.23, 129.29 (arom.-C), 133.60, 139.22 (q.-arom.-C), 171.82 (C3); MS (CI, *i*-butane): $m/z$ (%) = 232 (100) [$MH^+$]. Anal. calcd for $C_{14}H_{17}NS$ (231.1): C, 72.68; H, 7.41; N, 6.05; S, 13.86. Found: C, 72.50; H, 7.39; N, 5.95; S, 13.71%.

### 4.22. General procedure 3: enantioselective rhodium(I)-catalysed hydrosilylation of acetophenone

In a two-necked round bottomed flask the ligand (0.5 mmol) (see Table 1) was placed under an atmosphere of dry argon. After adding acetophenone (0.60 g, 5 mmol) and occasionally anhydrous solvent (1.5 mL) by syringe, the reaction flask was evacuated and filled with argon. The evacuation-argon purging procedure was repeated twice. $[Rh(cod)Cl]_2$ (6.2 mg, 0.0125 mmol) was added and the reaction mixture was stirred for 30 min. The flask was cooled to 0°C and diphenylsilane (0.96 g, 5.22 mmol) was added dropwise by syringe. After the addition the reaction mixture was slowly warmed to room temperature and stirring was continued at ambient temperature for 120 h. For work-up first methanol (3.5 mL) and then 2 M hydrochloric acid (9 mL) were added at 0°C. After stirring for a further 90 min in the ice-bath the acidic aqueous solution was extracted with diethyl ether (3×10 mL). The combined organic extracts were washed subsequently with saturated sodium hydrogen carbonate solution and brine (10 mL of each). After drying over magnesium sulphate the filtrate was concentrated in vacuo and the residue was purified by kugelrohr distillation (150°C, 13 mBar) to give the optically active secondary alcohol. The enantiomeric excess was determined by chiral GC (SGE Cydex-B, temperature program 100°C, 4°C $min^{-1}$ up to 140°C, 5 min isotherm; the retention times were (*R*)-1-phenylethan-1-ol 8.00 min, (*S*)-1-phenylethan-1-ol 8.20 min).

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