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Asymmetric Synthesis of 2-Heteroaryl Cyclic Amines: Total Synthesis of (–)-Anabasine

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A new and concise method for the synthesis of enantioenriched 2-heteroaryl cyclic amines was developed through an intramolecular chirality transfer. The influence of the nature of both ring size and heteroaryl moiety was investigated. The versatility of this reaction was demonstrated by the enantioselective synthesis of (–)-anabasine.

Introduction

Simple cyclic amines, namely piperidines and pyrrolidines, have been a target for many synthetic chemists because these ring systems are a common entity in many alkaloid natural products. They can also be regarded as privileged structures owing to their frequent appearance in multifarious bioactive substances.[1] Thus no fewer than 33 pyrrolidine or piperidine derivatives were on the list of top 200 prescription drugs in 2010 in the US market.[2] In particular, simple enantiopure 2-heteroaryl cyclic amines have become attractive scaffolds in medicinal chemistry. They exhibit significant biological activities and have been recently employed in the design of new pharmacophores with potential therapeutic applications. Representative examples are shown in Figure 1. For instance, this scaffold is present in natural product (–)-anabasine **I**, which is found in Tree Tobacco (*Nicotiana glauca*) and has been reported as a nicotinic acetylcholine agonist.[3] In addition, benzimidazole **II** is considered as a PARP-1 inhibitor,[4] whereas benzofuran derivative **III** displays high affinity for a4b2 nAChR.[5] Azepane framework **IV** has been recently reported as a prophylactic or therapeutic agent against cancer.[6]

Existing approaches for synthesizing cyclic amines with stereogenic centers at the C2 position are generally based on one of the following processes as the key step: ring-closing metathesis of disubstituted branches linked to a chiral amine,[7] asymmetric direct α-functionalization of the corresponding saturated cyclic amines,[2] asymmetric hydrogenation[8] or allylboration[9] of cyclic imines, addition to pyridinium salts bearing a chiral auxiliary,[10] and catalyzed asymmetric addition of diethylzinc to imines.[11] Thus, synthesis of enantiopure 2-substituted piperidine derivatives still constitutes an area of current interest and alternative methods are currently the object of intensive synthetic endeavors. The present study was carried out in connection with our on-going project on the development of efficient methodologies to generate original collections of new nitrogen-containing molecules.[12]

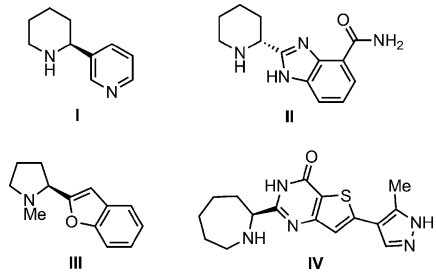

Figure 1. Examples of pharmacologically active 2-heteroaryl cyclic amines.

Results and Discussion

Our conceptually new synthetic methodology, which is depicted in retrosynthetic Scheme 1, is mainly based on the asymmetric reduction of endocyclic enehydrazide **5** and **6** bearing a (*S*)-methylprolinol chiral auxiliary (SMP).[13] Such precursors can be easily obtained from imide **7** and **8** through a palladium-catalyzed cross-coupling reaction.[14] The chiral SMP auxiliary has previously been used by Enders in the area of hydrazine and hydrazide chemistry and has proven to be more advantageous than the α-methylbenzyl group in related systems.[15] Recently, we have also reported the successful asymmetric reduction of endocyclic

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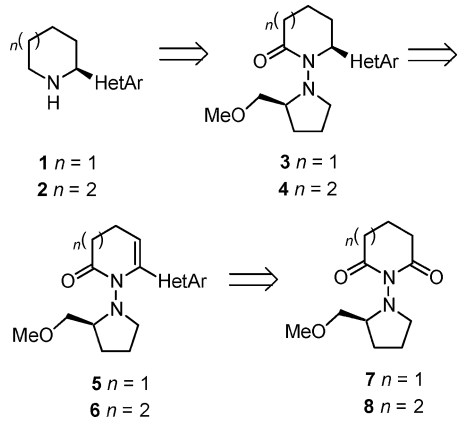
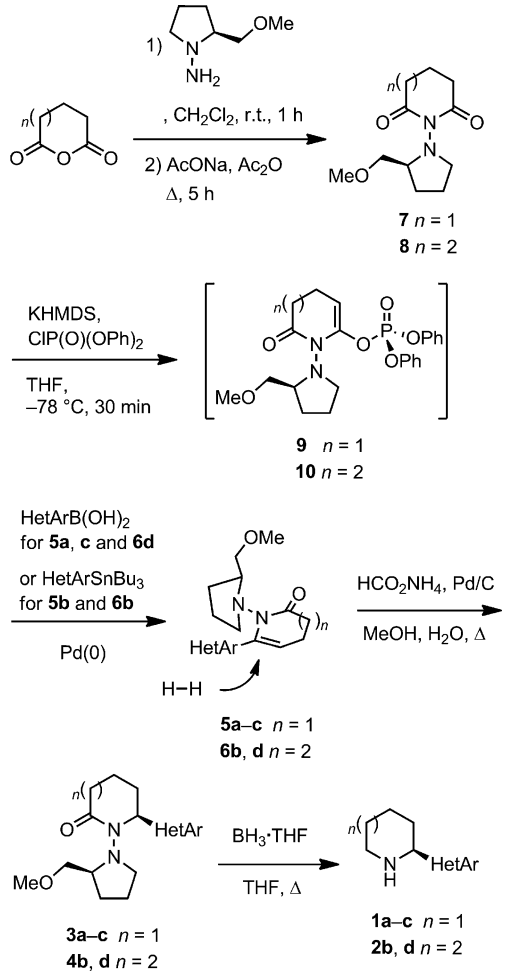
enamides in high yields and good stereoselectivity.[16] Finally, concomitant reductive N–N bond cleavage and ultimate reduction of the lactam carbonyl functionality (**3** and **4**) should provide desired chiral cyclic amine **1** and **2**.



Scheme 1. Retrosynthesis analysis for the preparation of chiral enantioenriched 2-heteroarylated cyclic amines.

The synthetic route, depicted in Scheme 2, required the preliminary elaboration of chiral imides **7** and **8**, which were easily prepared by condensation of the corresponding cyclic anhydrides and (*S*)-aminomethylprolinol.[17] We assumed that these cyclic imides would possess the appropriate functionality required for the connection of an additional heteroaryl unit through a palladium-mediated Suzuki–Miyaura cross-coupling reaction.[18] Since the pioneering work of Oshima et al.,[19] several groups have used constitutionally diverse enol phosphates in a variety of cross-coupling reactions.[20] Once installation of the stereocontrolling agent had been achieved, resulting chiral imides **7** and **8** were allowed to react with potassium bis(trimethylsilyl)amide (KHMDS) in the presence of diphenylchlorophosphate in THF to give mono vinyl phosphates **9** and **10**, which were used in the next step without further purification. Desired enehydrazides **5** and **6** were obtained in good yields over two steps by applying traditional Stille or Suzuki–Miyaura coupling conditions. Stille coupling was performed with the appropriate tin reagents in the presence of catalytic $Pd(PPh_3)_4$ and LiCl in THF at reflux temperatures. The Suzuki–Miyaura reaction was achieved by using boronic acids in combination with a catalytic amount of $PdCl_2(PPh_3)_2$, aqueous Na_2CO_3 and some drops of ethanol in THF heated to reflux. With a reliable route to these enehydrazides in hand, studies addressing the enantioselective preparation of 2-substituted piperidines and azepines **1** and **2** were initiated. For this purpose we first envisaged adopting a previously reported procedure,[21] which consists of treatment of enehydrazides **5** and **6** with trifluoroacetic acid and then with triethylsilane in sequence. Unfortunately no significant results could be obtained following this procedure. To obviate the lack of reactivity of our models toward hydride mediated reductions, we then envisaged reducing the enehydrazide endocyclic double bond through a catalytic asymmetric hydrogenation in the presence of Pd/C and ammonium formate[16] (Scheme 2).

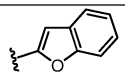
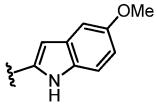
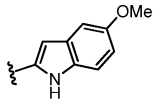
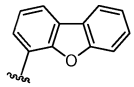


Scheme 2. Synthesis of 2-heteroaryl cyclic amines.

Our first attempt, performed with the six-membered ring models linked in C-2 with benzofuran entity **5a**, indole derivative **5b** and furan entity **5c**, delivered lactam intermediates **3a**–**3c** in high yield and good diastereoselectivity (Table 1). The two diastereoisomers were detectable by ^1H NMR spectrometry. Isomer *S* was the main isomer obtained, probably because the hydrogen source can preferentially attack from the most sterically free face.[16] Most interestingly, the seven-member ring bearing indole and dibenzofuran group **6b** and **6d** afforded reduced compound **3b** and **3d** in good yield as a single pure diastereoisomer. No trace of the second isomer was detected by ^1H NMR spectrometry (*de* > 96% after chromatographic treatment), that demonstrates the high selectivity in the reduction of unsaturated compounds **6b** and **6d**. Finally, reductive N–N bond cleavage with a BH_3·THF complex[22] was accomplished through the concomitant reduction of the lactam carbonyl moiety to conclude the synthesis and this operation afforded desired enantioenriched 2-heteroaryl cyclic amines **1a**–**1c** and **2b** and **2d**.

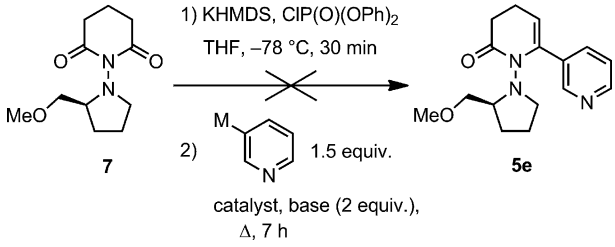
With this feasible methodology in hand we then turned our attention to the total synthesis of exemplary representative natural product (*S*)-(–)-anabasine **1e**, which belongs to the large group of piperidine alkaloids containing a 3-pyr-

Table 1. Yields of intermediates **5**, **6** and **3**, **4** and of the 2-heteroaryl cyclic amines **1**, **2**.

Entry	*n*	HetAr	Enehydrazides	Yield[a] (%)	Lactams	Yield[a] (%)	*de*[b] (%)	Cyclic amines	Yield[a] (%)	*ee*[c] (%)
1	1		**5a**	54	**3a**	88	86	**1a**	80	86
2	1		**5b**	57	**3b**	94	82	**1b**	87	82
3	1		**5c**	49	**3c**	85	84	**1c**	69	84
4	2		**6b**	67	**4b**	84	>96	**2b**	82	>96
5	2		**6d**	72	**4d**	86	>96	**2d**	79	>96

[a] Isolated yields after purification by column chromatography. [b] Determined by ^{1}H NMR spectroscopy. [c] Correlated to the value of corresponding lactams **3** and **4** assuming that the deprotection takes place without detectable racemization.[22]

idyl substituent in the 2-position of the piperidine ring. Although structurally not very complex, only a limited number of stereocontrolled total syntheses of this natural product have been reported.[23] According to the previously described procedure, we first planned to synthesize enehydrazide precursor **5e** equipped with a pyridin-3-yl unit from parent chiral imide **7** (Scheme 3).



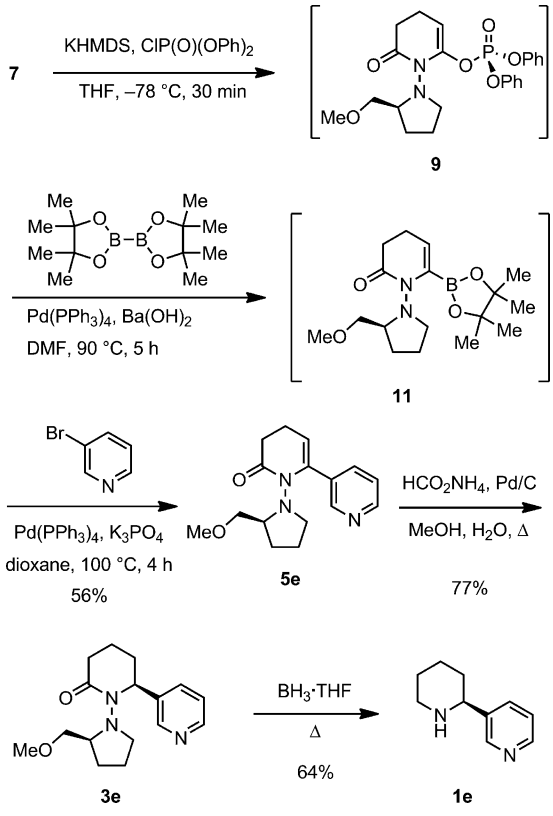
Scheme 3. Attempts towards the synthesis of chiral enehydrazide 5e.

Somewhat disappointingly, imide **7** was not amenable to the cross-coupling reaction conditions likely to give access to required 6-hetarylated compound **5e** even after considerable experimentation with various catalysts, bases and solvents (Table 2).

Table 2. Conditions for the cross-coupling reaction.

Entry	M	Catalyst	Base or additive	Solvent
1	$B(OH)_2$	$Pd(PPh_3)_4$	Na_2CO_3	THF, H_2O
2	$B(OH)_2$	$PdCl_2(PPh_3)_2$	Na_2CO_3	DME, H_2O
3	$B(OH)_2$	$PdCl_2(PPh_3)_2$	Cs_2CO_3	DMF
4	$B(OH)_2$	$Pd(PPh_3)_4$	K_3PO_4	dioxane
5	$SnBu_3$	$Pd(PPh_3)_4$	LiCl	THF

One can reasonably assume that this failure is attributable to the lack of reactivity of electron-poor boronic acids towards Suzuki–Miyaura and Stille cross-coupling reactions. Consequently, we decided to adopt an alternative strategy for the installation of the pyridine-3-yl unit depicted in Scheme 4, which is based upon an umpolung of the phosphate electrophile by α-borylation.[24]



Scheme 4. Total synthesis of (–)-anabasine.

Following a procedure reported by Occhiato et al.,[24a] the conversion of vinyl phosphate **9** into the corresponding boronate was first realized by the Pd-catalyzed coupling with commercial bis(pinacolato)diboron. The best protocol was made use of $Pd(PPh_3)_4$ as a catalyst with finely powdered $Ba(OH)_2$ as base in anhydrous DMF at 90 °C. The reaction was complete within 5 h and furnished aminovinyl boronate **11**, which was used without further purification in the next step. Heterocyclic boronate **11** was then success-

fully engaged in a Suzuki–Miyaura cross-coupling reaction to furnish targeted enehydrazide **5e**. Catalytic hydrogenation with Pd on C with ammonium formate proceeded uneventfully to provide an excellent yield of corresponding cyclic hydrazide (*S*,*S*)-**3e**. NMR spectroscopic investigations after chromatographic separation indicated the presence of a single diastereomer, thus confirming the high level of diastereoselectivity observed in the catalytic hydrogenation of unsaturated compound **5e**. Treatment with borane–THF complex of (*S*,*S*)-**3e** effected reductive N–N bond cleavage with the concomitant reduction of the lactam carbonyl group to afford targeted natural product **1e** (Scheme 4). The absolute configuration of the stereogenic center was confirmed to be (*S*) from the sign of the specific rotation of **1e**, and the enantiopurity of our synthetic (*S*)-(–)-anabasine **1e** was clearly established from the optical rotation and spectroscopic data that matched with those reported for the natural product.[23b]

Conclusions

In conclusion, a new strategy has been developed and successfully employed for the asymmetric synthesis of a variety of 2-heteroaryl cyclic amines. The key step is based upon the diastereoselective reduction of enehydrazides equipped with Enders chiral auxiliary. In addition, this protocol shows great flexibility regarding ring size and heteroaryl groups. The utility of our synthetic protocol is illustrated by the total synthesis of (*S*)-(–)-anabasine, an alkaloid extracted from *Nicotiana glauca*. The extension of this approach to other scaffolds is in progress in our laboratory.

Experimental Section

General: The reactions were performed with dried glassware under an atmosphere of dry argon. Dimethyl sulfoxide was distilled from molecular sieves (4 Å), CH_2Cl_2 was dried by heating to reflux over CaH_2 and then distilled, and toluene was distilled from sodium. Reactions were monitored by thin layer chromatography (TLC) by using Sorbent Technologies 0–20 mm silica gel 60 Å plates. TLC spots were viewed under ultraviolet light and by heating the plate after treatment with an appropriate revelatory agent ($KMnO_4$, phosphomolybdic acid). Purifications by column chromatography were performed with Sorbent Technologies 32–63 μm silica gel (60 Å). NMR Spectra were recorded with a Bruker AM 300 MHz or 400 MHz spectrometers. Chemical shifts are given in ppm (δ) and referenced to the internal solvent signal or to tetramethylsilane used as an internal standard. Multiplicities are declared as follows: s (singlet), br. s (broad singlet), d (doublet), t (triplet), quint (quintuplet), sept (septet), dd (doublet of doublet), ddd (doublet of doublet of doublet), dt (doublet of triplet), ABq (ABq system), m (multiplet). IR absorption spectra were obtained with a Nicolet 380 FTIR. Optical rotations were recorded with a Perkin–Elmer 343. Melting points were obtained with a Reichert-Thermopan apparatus. HRMS were recorded with a Maxis Bruker 4G instrument.

General Procedure for the Preparation of Cyclic Hydrazimides 7 and 8: Cyclic hydrazimides **7** and **8** were prepared according to a reported procedure[16] starting from (*S*)-1-Amino-2-(methoxymethyl)-pyrrolidine[25] (3.91 g, 0.03 mol) and commercial glutaric anhydride (3.42 g, 0.03 mol) or adipic anhydride[26] (3.84 g, 0.03 mol).

(*S*)-1-[2-(Methoxymethyl)pyrrolidin-1-yl]azepane-2,7-dione (8): Yield 5.62 g, 78% as a colorless oil. R_f = 0.35 (EtOAc/PE, 7:3). $[\alpha]_D^{20}$ = –37.3 (c = 1.50, $CHCl_3$). IR (diamond-ATR, neat): $\tilde{\nu}_{max}$ = 1682 (C=O), 1126 (C–O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.51–1.57 (m, 1 H, CH_2), 1.66–1.99 (m, 8 H, 4 × CH_2), 2.53–2.65 (m, 4 H, 2 × CH_2), 3.12–3.29 (m, 7 H), 3.58–3.67 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3 (CH_2), 20.7 (CH_2), 22.6 (CH_2), 27.2 (CH_2), 35.4 (CH_2), 36.1 (CH_2), 51.3 (CH_2), 58.7 (CH_3O), 59.8 (CH), 77.1 (CH_2), 174.2 (CO), 176.5 (CO) ppm. MS (IS): m/z = 241.0 $[M + H]^+$, 263.0 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{12}H_{21}N_2O_3$ $[M + H]^+$ 241.1546; found 214.1542.

General Procedure for the Suzuki–Miyaura Cross-Coupling and the Preparation of Enehydrazides 5a, 5c and 6d: To a solution of imide **7** and **8** (2 mmol) and diphenylphosphoryl chloride (0.62 mL, 3 mmol) in anhydrous THF (30 mL) cooled to –78 °C and under nitrogen atmosphere, was added dropwise whilst stirring a solution of KHMDS (6 mL, 0.5 M in toluene, 3 mmol). After 30 min at –78 °C, water (20 mL) was added and the resulting mixture was extracted with Et_2O (2 × 50 mL) and dried with $MgSO_4$. Evaporation of the solvent under vacuum yielded **9** and **10** as a yellow oil, which were directly used for the next coupling step.

To a stirred solution of crude **9** and **10** (2 mmol) in THF (20 mL) maintained under a nitrogen atmosphere, were added 2 M aqueous Na_2CO_3 solution (2 mL, 4 mmol), $Pd(PPh_3)_4$ (120 mg, 5 mol-%) and the appropriate aromatic boronic acid (3 mmol). The mixture was stirred for 2 h at reflux temperatures, and was then diluted with water (2 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried with $MgSO_4$, concentrated under vacuum and purified by flash column chromatography with EtOAc/PE as eluent to afford enhydrazides **5a**, **5c** and **6d**.

(*S*)-6-(Benzofuran-2-yl)-1-[2-(methoxymethyl)pyrrolidin-1-yl]-3,4-dihydropyridin-2(1*H*)-one (5a): Yield 352 mg, 54% as a yellow oil. R_f = 0.57 (EtOAc/PE, 3:7). $[\alpha]_D^{20}$ = –57.2 (c = 0.10, $CHCl_3$). IR (diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2873 (CH), 1682 (C=O), 1452 (C=C) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.38–1.45 (m, 1 H, CH_2), 1.64–1.72 (m, 1 H, CH_2), 1.95–2.01 (m, 1 H, CH_2), 2.03–209 (m, 1 H, CH_2), 2.31–2.40 (m, 1 H, CH_2), 2.45–2.50 (m, 1 H, CH_2), 2.53–2.61 (m, 2 H, CH_2), 3.12–3.18 (m, 1 H, CH_2), 3.14 (s, 3 H, OCH_3), 3.17–3.21 (m, 1 H, CH_2), 3.29–3.36 (m, 1 H, CH_2), 3.59 (q, J = 8.0 Hz, 1 H, CH_2), 3.87 (qt, J = 6.5 Hz, 1 H, CH), 5.88 (q, J = 3.2 Hz, 1 H, CH=), 6.92 (s, 1 H, ArH), 7.18–7.28 (m, 2 H, ArH), 7.43 (d, J = 8.1 Hz, 1 H, ArH), 7.56 (d, J = 7.2 Hz, 1 H, H_{arom}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.9 (CH_2), 23.0 (CH_2), 28.0 (CH_2), 33.5 (CH_2), 51.7 (CH_2), 58.9 (OCH_3), 60.7 (CH), 76.5 (CH_2), 105.4 (CH), 109.4 (CH=), 111.0 (CH), 121.3 (CH), 122.9 (CH), 124.6 (CH), 128.9 (C), 136.9 (C), 151.3 (C), 154.3 (C), 169.4 (CO) ppm. MS (IS): m/z = 327.0 $[M + H]^+$, 349.0 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{19}H_{23}N_2O_3$ $[M + H]^+$ 327.1702; found 327.1710.

(*S*)-6-(Furan-2-yl)-1-[2-(methoxymethyl)pyrrolidin-1-yl]-3,4-dihydropyridin-2(1*H*)-one (5c): Yield 270 mg, 49% as a colorless oil. R_f = 0.73 (EtOAc/PE, 5:5). $[\alpha]_D^{20}$ = –59.7 (c = 1.81, $CHCl_3$). IR (diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2970 (CH), 2885 (CH), 1666 (C=O), 1465 (C=C), 1087 (C–O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.41–1.51 (m, 1 H, CH_2), 1.61–1.74 (m, 1 H, CH_2), 1.90–2.14 (m, 2 H, CH_2), 2.20–2.31 (m, 1 H, CH_2), 2.36–2.59 (m, 3 H, CH_2), 3.06–3.20 (m, 6 H), 3.50–3.58 (q, J = 8 Hz, 1 H), 3.79–3.87 (m, 1 H), 5.61–5.64 (m, 1 H, CH=), 6.36–6.38 (m, 1 H, ArH), 6.52–6.53 (m, 1 H, ArH), 7.36 (m, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.5 (CH_2), 22.8 (CH_2), 27.8 (CH_2), 33.3 (CH_2), 51.3

(CH_2), 58.7 (CH_3O), 60.3 (CH), 76.2 (CH_2), 106.7 (CH), 108.8 (CH), 110.8 (CH), 136.6 (C), 141.5 (CH), 149.0 (C), 169.5 (CO) ppm. MS (IS): m/z = 277.0 $[M + H]^+$, 299.0 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{15}H_{21}N_2O_3$ $[M + H]^+$ 277.1546; found 277.1545.

(*S*)-7-(Dibenzo[*b*,*d*]furan-4-yl)-1-[2-(methoxymethyl)pyrrolidin-1-yl]-1,3,4,5-tetrahydroazepin-2-one (6d): Yield 562 mg, 72% as a yellow oil. R_f = 0.41 (EtOAc/PE, 3:7). $[\alpha]_D^{20}$ = –76.6 (c = 1.84, $CHCl_3$). IR (diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2868 (CH), 1673 (C=O), 1454 (C=C), 1108 (C–O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.33–1.44 (m, 2 H, CH_2), 1.81–1.89 (m, 1 H, CH_2), 2.05–2.17 (m, 2 H, CH_2), 2.26–2.65 (m, 5 H, CH_2), 2.74–2.92 (m, 2 H), 3.11–3.15 (m, 4 H), 3.41–3.49 (m, 1 H), 3.84 (br. s, 1 H), 6.02 (t, J = 7.5 Hz, 1 H, CH=), 7.30–7.47 (m, 4 H, ArH), 7.54–7.56 (m, 1 H, ArH), 7.87–7.95 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.5 (CH_2), 24.1 (CH_2), 28.7 (CH_2), 30.8 (CH_2), 34.8 (CH_2), 51.7 (CH_2), 58.8 (CH_3O), 62.4 (CH), 76.0 (CH_2), 111.8 (CH), 120.1 (CH), 120.7 (CH), 121.4 (CH), 122.6 (CH), 122.9 (CH), 123.1 (C), 124.1 (C), 124.4 (C), 127.2 (CH), 127.3 (CH), 141.5 (C), 153.5 (C), 155.9 (C), 174.2 (CO) ppm. MS (IS): m/z = 391.0 $[M + H]^+$, 413.0 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{24}H_{27}N_2O_3$ $[M + H]^+$ 391.2015; found 391.2009.

General Procedure for the Stille Cross-Coupling and the Preparation of Enhydrazides 5b, 6b: Synthesis of the organic tin compound [tributyl(5-methoxy-1*H*-indol-2-yl)tin]: To a solution of 5-methoxy-1*H*-indole (12.20 g, 83.0 mmol) in dry THF (30 mL) at –78 °C was added *n*BuLi (1.6 M, 56.9 mL, 91.0 mmol) over a 15 min period. The reaction mixture was warmed to room temperature, stirred for 1 h and then re-cooled to –78 °C. Benzenesulfonyl chloride (11.6 mL, 91.0 mmol) was added and the reaction mixture was warmed to room temperature and stirred for 16 h. Saturated sodium hydrogen carbonate solution (50 mL) was added and the mixture extracted with diethyl ether (2 × 50 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried ($MgSO_4$), and concentrated in vacuo. Crystallization from hexane/Et_2O (2:1) afforded 5-methoxy-(1-phenylsulfonyl)-1*H*-indole (19.06 g, 80%).

To a solution of 5-methoxy-(1-phenylsulfonyl)-1*H*-indole (6.14 g, 21.4 mmol) in dry THF (10 mL) at –78 °C was added a solution of lithium diisopropylamide in THF/hexanes (1.0 M, 22.5 mL, 22.5 mmol). The reaction mixture was stirred at –78 °C for 30 min, then at 0 °C for 30 min, then re-cooled to –78 °C. Tri-*n*-butyltin chloride (5.79 mL, 21.4 mmol) was added and the reaction mixture stirred at –78 °C for 1 h, then at 0 °C for 1 h. Saturated ammonium chloride solution (20 mL) was added and the mixture extracted with diethyl ether (3 × 15 mL). The combined organic extracts were washed with water (2 × 20 mL), dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (EtOAc/PE, 1:99) yielded 2-tri-*n*-butylstannyl-5-methoxy-(1-phenylsulfonyl)-1*H*-indole (5.30 g, 43%) as a colorless oil.

2-Tri-*n*-butylstannyl-5-methoxy-(1-phenylsulfonyl)-1*H*-indole (4.00 g, 6.94 mmol) was dissolved in a mixture of dry THF (30 mL) and dry MeOH (30 mL) under argon at –30 °C. To this solution was added disodium hydrogen phosphate (2.16 g, 15.26 mmol) followed by Na(Hg) amalgam (5–6%; 3.40 g, 15.26 mmol) and the resulting mixture was stirred 2 h at 0 °C before filtration through Celite. After addition of water, the aqueous layer was extracted with EtOAc and the combined organic extracts were washed with brine, dried with $MgSO_4$, filtered and concentrated. The tributyl(5-methoxy-1*H*-indol-2-yl)tin (yellow oil, 2.21 g, 73%) was used for the next step without further purification.

To a stirred solution of crude vinyl phosphates **9** and **10** (2 mmol) in anhydrous THF (40 mL) maintained under nitrogen atmosphere, were added LiCl (255 mg, 6 mmol), $Pd(PPh_3)_4$ (114 mg, 5 mol-%) and tributyl(5-methoxy-1*H*-indol-2-yl)tin (1.31 g, 3 mmol). The mixture was stirred for 16 h at reflux temperatures, and then it was diluted with water (2 mL) and extracted with EtOAc (3 × 40 mL). The combined organic layers were dried with $MgSO_4$, concentrated under vacuum and purified by flash column chromatography with EtOAc/PE (3:7) as eluent to afford enhydrazide **5b** and **6b**.

(*S*)-6-(5-Methoxy-1*H*-indol-2-yl)-1-[(2-methoxymethyl)pyrrolidin-1-yl]-3,4-dihydro-1*H*-pyridin-2-one (5b): Yield 405 mg, 57% as a colorless oil. R_f = 0.23 (EtOAc/PE, 3:7). $[\alpha]_D^{20}$ = –27.9 (c = 0.10, $CHCl_3$). IR (diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3295 (NH), 2941 (CH), 2876 (CH), 1680 (C=O), 1486 (C=C) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.65–1.71 (m, 1 H, CH_2), 1.79–1.94 (m, 2 H, CH_2), 2.12–2.18 (m, 1 H, CH_2), 2.28–2.39 (m, 2 H, CH_2), 2.59–2.68 (m, 2 H, CH_2), 2.82 (td, J = 7.4, 4.0 Hz, 1 H, CH_2), 3.33 (q, J = 8.0 Hz, 1 H, CH), 3.39 (dd, J = 10.1, 3.2 Hz, 1 H, CH), 3.44 (s, 3 H, OCH_3), 3.55 (dd, J = 10.0, 2.3 Hz, 1 H, CH_2), 3.85 (s, 3 H, OCH_3), 4.07–4.12 (m, 1 H, CH), 5.63 (q, J = 3.8 Hz, 1 H, CH=), 6.51 (d, J = 1.5 Hz, 1 H, ArH), 6.83 (dd, J = 8.8, 2.4 Hz, 1 H, ArH), 7.04 (d, J = 2.2 Hz, 1 H, ArH), 7.22 (d, J = 8.8 Hz, 1 H, ArH), 10.9 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3 (CH_2), 23.7 (CH_2), 26.9 (CH_2), 33.6 (CH_2), 51.7 (CH_2), 56.1 (OCH_3), 58.9 (OCH_3), 60.5 (CH), 74.0 (CH_2), 101.8 (CH), 102.1 (CH), 108.8 (CH=), 112.0 (CH), 112.7 (CH), 127.8 (C), 132.1 (C), 134.2 (C), 137.0 (C), 154.2 (C), 170.0 (CO) ppm. MS (IS): m/z = 356.0 $[M + H]^+$. HRMS (ESI): calcd. for $C_{20}H_{26}N_3O_3$ $[M + H]^+$ 356.1965; found 356.1971.

(*S*)-7-(5-Methoxy-1*H*-indol-2-yl)-1-[2-(methoxymethyl)pyrrolidin-1-yl]-1,3,4,5-tetrahydroazepin-2-one (6b): Yield 494 mg, 67% as a brown film. R_f = 0.27 (EtOAc/PE, 3:7). $[\alpha]_D^{20}$ = –39.1 (c = 0.10, $CHCl_3$). IR (diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3303 (NH), 2946 (CH), 2866 (CH), 1670 (C=O), 1450 (C=C), 1113 (C–O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.52–1.59 (m, 1 H, CH_2), 1.67–1.75 (m, 1 H, CH_2), 1.90–1.97 (m, 1 H, CH_2), 2.08–2.15 (m, 1 H, CH_2), 2.18–2.26 (m, 2 H, CH_2), 2.31–2.36 (m, 2 H, CH_2), 2.46–2.55 (m, 2 H, CH_2), 3.13–3.20 (m, 1 H, CH_2), 3.32–3.41 (m, 6 H, CH, CH_2 and OCH_3), 3.85 (s, 3 H, OCH_3), 4.22 (br., 1 H, CH), 6.14 (t, J = 7.7 Hz, 1 H, CH=), 6.55 (s, 1 H, ArH), 6.82 (dd, J = 8.8, 2.4 Hz, 1 H, ArH), 7.05 (s, 1 H, ArH), 7.23 (d, J = 8.8 Hz, 1 H, ArH), 10.01 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.0 (CH_2), 24.2 (CH_2), 27.8 (CH_2), 30.1 (CH_2), 34.9 (CH_2), 52.1 (CH_2), 56.1 (OCH_3), 59.0 (OCH_3), 60.2 (CH), 76.0 (CH_2), 100.4 (CH), 102.0 (CH), 112.0 (CH), 112.5 (CH), 120.5 (CH=), 128.6 (CH), 130.1 (CH), 131.6 (CH), 136.4 (CH), 154.4 (CH), 175.4 (CO) ppm. MS (IS): m/z = 370.0 $[M + H]^+$. HRMS (ESI): calcd. for $C_{21}H_{28}N_3O_3$ $[M + H]^+$ 370.2121; found 370.2119.

General Procedure for the Preparation of Cyclic Hydrazides 3 and 4: A suspension of compound **5** and **6** (0.5 mmol) in MeOH (10 mL) was stirred with activated Pd/C (10%, 20 mg) and a solution of HCO_2NH_4 (315 mg, 5 mmol) in distilled water (2 mL) was then added. The reaction mixture was heated to reflux for 4 h, filtered through Celite™ and diluted with water. Extraction with CH_2Cl_2 (3 × 20 mL), drying over $MgSO_4$ and concentration under vacuum left an oily product, which was purified by chromatography on silica gel with EtOAc/EP (6:4) as eluent to give **3** and **4**.

(*S*)-6-(Benzofuran-2-yl)-1-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-piperidin-2-one (3a): Yield 144 mg, 88% as a colorless oil. R_f = 0.23 (EtOAc/PE, 5:5). $[\alpha]_D^{20}$ = –83.4 (c = 0.10, $CHCl_3$). IR (diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2949 (CH), 2872 (CH), 1651 (C=O), 1453 (C=C), 1011 (C–O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.53–1.58 (m, 1 H, CH_2), 1.65–1.90 (m, 3 H, CH and CH_2), 2.01–2.08 (m, 1 H, CH_2), 2.15–2.25 (m, 3 H, CH and CH_2), 2.40–2.64 (m, 4

H, 2×CH_2), 2.77 (br. s, 3 H, OCH_3), 3.16–3.24 (m, 2 H, CH_2), 3.70 (br., 1 H, CH), 4.83 (t, J = 4.3 Hz, 1 H, CH), 6.62 (s, 1 H, CH), 7.20–7.27 (m, 2 H, ArH), 7.46 (d, J = 8.0 Hz, 1 H, ArH), 7.54 (d, J = 7.0 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.2 (CH_2), 23.2 (CH_2), 27.8 (CH_2), 29.9 (CH_2), 33.9 (CH_2), 51.0 (CH_2), 58.6 (OCH_3), 60.1 (CH), 60.7 (CH), 75.5 (CH_2), 104.9 (CH), 111.4 (CH), 121.0 (CH), 123.1 (CH), 124.3 (CH), 128.3 (C), 154.7 (C), 157.8 (C), 169.7 (CO) ppm. MS (IS): m/z = 329.0 $[M + H]^+$, 351.0 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{19}H_{25}N_2O_3$ $[M + H]^+$ 329.1859; found 329.1851.

(*S*)-7-(5-Methoxy-1*H*-indol-2-yl)-1-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]azepan-2-one (3b): Yield 168 mg, 94% as a yellow oil. R_f = 0.28 (EtOAc/PE, 9:1). $[\alpha]_D^{20}$ = –38.1 (c = 0.10, $CHCl_3$). IR (diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3270 (NH), 2929 (CH), 1629 (C=O), 1442 (C=C), 1089 (C–O) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.43–1.50 (m, 1 H, CH_2), 1.65–2.01 (m, 4 H, 2×CH_2), 2.09–2.18 (m, 2 H, 2×CH), 2.23–2.29 (m, 1 H, CH_2), 2.34–2.50 (m, 2 H, H_3), 2.86–2.98 (m, 1 H, CH_2), 3.01 (dd, J = 10.0, 4.0 Hz, 1 H, CH_2), 3.22 (s, 3 H, OCH_3), 3.26–2.35 (m, 2 H, CH_2), 3.84 (s, 3 H, OCH_3), 4.10–4.15 (m, 1 H, CH), 4.88 (t, J = 5.0 Hz, 1 H, CH), 6.31 (s, 1 H, ArH), 6.81 (dd, J = 8.7, 2.3 Hz, 1 H, H_{arom}), 7.04 (d, J = 2.2 Hz, 1 H, ArH), 7.23 (d, J = 8.8 Hz, 1 H, ArH), 9.57 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.6 (CH_2), 23.3 (CH_2), 27.5 (CH_2), 30.7 (CH_2), 33.9 (CH_2), 51.4 (CH_2), 56.1 (OCH_3), 59.0 (OCH_3), 59.5 (CH), 60.0 (CH), 76.4 (CH_2), 99.9 (CH), 102.2 (CH), 111.9 (CH), 112.0 (CH), 128.9 (C), 131.5 (C), 140.4 (C), 154.3 (C), 171.0 (CO) ppm. MS (IS): m/z = 358.0 $[M + H]^+$, 380.0 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{20}H_{28}N_3O_3$ $[M + H]^+$ 358.2121; found 358.2125.

(*S*)-6-(Furan-2-yl)-1-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]piperidin-2-one (3c): Yield 118 mg, 85% as a colorless oil. R_f = 0.35 (EtOAc/PE, 5:5). $[\alpha]_D^{20}$ = –36.2 (c = 1.59, $CHCl_3$). IR (diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2962 (CH), 2877 (CH), 1651 (C=O), 1396 (C=C), 1111 (C–O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47–1.65 (m, 3 H, CH_2), 1.70–1.82 (m, 1 H, CH_2), 1.87–2.01 (m, 3 H, CH_2), 2.06–2.12 (m, 1 H, CH_2), 2.27–2.52 (m, 4 H, CH_2), 3.04–3.11 (m, 5 H), 3.57–3.68 (m, 1 H), 4.60–4.63 (t, J = 4.5 Hz, 1 H, NCH), 6.14–6.18 (m, 1 H, ArH), 6.28–6.30 (m, 1 H, ArH), 7.32–7.40 (m, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.9 (CH_2), 23.3 (CH_2), 27.7 (CH_2), 29.9 (CH_2), 33.6 (CH_2), 50.7 (CH_2), 58.3 (CH_3O), 59.6 (CH), 60.5 (CH), 75.3 (CH_2), 107.8 (CH), 110.1 (CH), 141.7 (CH), 154.8 (C), 169.2 (CO) ppm. MS (IS): m/z = 279.0 $[M + H]^+$, 301.0 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{15}H_{23}N_2O_3$ $[M + H]^+$ 279.1702; found 279.1695.

(*S*)-7-(5-Methoxy-1*H*-indol-2-yl)-1-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]azepan-2-one (4b): Yield 156 mg, 84% as a brown solid, m.p. 89–91 °C. R_f = 0.54 (EtOAc/PE, 6:4). $[\alpha]_D^{20}$ = –42.9 (c = 0.11, $CHCl_3$). IR (diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3270 (NH), 2929 (CH), 1629 (C=O), 1442 (C=C), 1089 (C–O) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.34–1.96 (m, 11 H, CH and 5×CH_2), 2.46–2.55 (m, 1 H, CH_2), 3.07 (td, J = 7.6, 2.8 Hz, 1 H, CH_2), 3.31–3.45 (m, 2 H, 2×CH), 3.51–3.60 (m, 4 H, CH_2 and OCH_3), 3.79 (s, 3 H, OCH_3), 4.20–4.28 (m, 1 H, CH), 5.16–5.25 (m, 1 H, CH), 6.28 (s, 1 H, ArH), 6.84 (dd, J = 8.7, 2.5 Hz, 1 H, ArH), 7.06 (d, J = 2.4 Hz, 1 H, ArH), 7.24 (d, J = 2.8 Hz, 1 H, ArH), 10.38 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.8 (CH_2), 23.8 (CH_2), 25.2 (CH_2), 27.4 (CH_2), 31.5 (CH_2), 37.0 (CH_2), 53.1 (CH_2), 56.1 (OCH_3), 58.9 (OCH_3), 60.5 (CH), 63.6 (CH), 78.3 (CH_2), 99.9 (CH), 102.2 (CH), 111.7 (CH), 111.8 (CH), 128.9 (C), 131.9 (C), 138.4 (C), 154.1 (C), 175.0 (CO) ppm. MS (IS): m/z = 372.0 $[M + H]^+$, 394.0 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{21}H_{29}N_3O_3$ $[M + H]^+$ 372.2278; found 372.2286.

(*S*)-7-(Dibenzo[*b*,*d*]furan-4-yl)-1-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]azepan-2-one (4d): Yield 168 mg, 86% as a colorless oil. R_f = 0.25 (EtOAc/PE, 5:5). $[\alpha]_D^{20}$ = –24.6 (c = 1.49, $CHCl_3$). IR (diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2970 (CH), 2901 (CH), 1651 (C=O), 1404 (C=C), 1057 (C–O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34–1.59 (m, 3 H, CH_2), 1.65–1.90 (m, 4 H, CH_2), 2.01–2.10 (m, 1 H, CH_2), 2.23–2.32 (m, 1 H, CH_2), 2.60–2.64 (m, 2 H, CH_2), 2.77–2.81 (m, 1 H), 2.92–3.04 (m, 3 H), 3.23 (s, 3 H, OCH_3), 3.58–3.61 (m, 1 H), 3.86 (br. s, 1 H), 5.52–5.56 (m, 1 H, NCH), 7.31–7.39 (m, 3 H, ArH), 7.44–7.50 (t, J = 9 Hz, 1 H, ArH), 7.57–7.60 (d, J = 9 Hz, 1 H, ArH), 7.87–7.90 (d, J = 9 Hz, 1 H, ArH), 7.95–7.98 (d, J = 9 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.9 (CH_2), 23.3 (CH_2), 25.0 (CH_2), 27.3 (CH_2), 32.1 (CH_2), 37.4 (CH_2), 51.5 (CH_2), 58.9 (CH_3O), 60.8 (CH), 65.8 (CH), 76.4 (CH_2), 111.7 (CH), 119.5 (CH), 120.7 (CH), 122.6 (CH), 122.9 (CH), 124.1 (C), 124.4 (C), 125.2 (C), 125.9 (CH), 127.2 (CH), 153.2 (C), 155.9 (C), 174.1 (CO) ppm. MS (IS): m/z = 393.0 $[M + H]^+$, 414.0 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{24}H_{29}N_2O_3$ $[M + H]^+$ 393.2172; found 393.2169.

General Procedure for Synthesis of Heteroaryl Cyclic Amines 1 and 2: A solution of borane–THF complex (1.0 M solution in THF, 5 mL, 5 mmol) was added at 0 °C to a stirred solution of **3** and **4** (0.25 mmol) in THF (10 mL). The solution was stirred at room temperature for 15 min and then heated to reflux for 24 h. After the mixture was cooled in an ice-bath, 10% aqueous NaOH (10 mL) was added and the mixture was briefly stirred (5 min). The mixture was extracted with Et_2O (3 × 10 mL). The combined extracts were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (acetone/MeOH, 9:1) to give **1** and **2**.

(*S*)-2-(Benzofuran-2-yl)piperidine (1a): Yield 40 mg, 80% as a yellow film. R_f = 0.18 (acetone/MeOH, 9:1). $[\alpha]_D^{20}$ = –22.2 (c = 0.51, $CHCl_3$). IR (diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3301 (NH), 2929 (CH), 2854 (CH), 1554 (C=C), 1253 (C–O) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.67–2.16 (m, 5 H, 2×CH_2 and NH), 2.33–2.40 (m, 2 H, CH_2), 2.82 (t, J = 10.4 Hz, 1 H, CH_2), 3.19 (d, J = 11.6 Hz, 1 H, CH_2), 3.91 (d, J = 8.1 Hz, 1 H, CH), 6.57 (s, 1 H, ArH), 7.18–7.23 (m, 2 H, ArH), 7.44–7.49 (m, 1 H, ArH), 7.52–7.58 (m, 1 H, ArH) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 24.4 (CH_2), 26.0 (CH_2), 31.1 (CH_2), 46.9 (CH_2), 55.1 (CH), 101.8 (CH), 111.3 (CH), 121.0 (CH), 122.8 (CH), 123.9 (CH), 128.5 (C), 154.8 (C), 160.2 (C) ppm. MS (IS): m/z = 202.0 $[M + H]^+$. HRMS (ESI): calcd. for $C_{13}H_{16}NO$ $[M + H]^+$ 202.1229; found 202.1236.

(*S*)-5-Methoxy-2-piperidin-2-yl-1*H*-indole (1b): Yield 50 mg, 87% as a yellow oil. R_f = 0.11 (acetone/MeOH, 9:1). $[\alpha]_D^{20}$ = –9.5 (c = 0.10, $CHCl_3$). IR (diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3234 (NH), 2929 (CH), 1589 (C=C), 1487 (C=C), 1454 (C=C) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47–1.65 (m, 4 H, CH, CH_2 and NH), 1.91–2.08 (m, 3 H, CH and CH_2), 2.69–2.75 (m, 1 H, CH_2), 2.97–3.06 (m, 1 H, CH_2), 3.81 (s, 3 H, OCH_3), 4.00 (d, J = 10.2 Hz, 1 H, CH), 6.33 (s, 1 H, ArH), 6.81 (dd, J = 8.8, 2.4 Hz, 1 H, ArH), 6.96 (d, J = 1.8 Hz, 1 H, ArH), 7.22 (d, J = 8.8 Hz, 1 H, ArH), 6.65 (br. s, 1 H, NH) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 23.3 (CH_2), 23.8 (CH_2), 29.9 (CH_2), 45.5 (CH_2), 54.7 (CH), 56.6 (OCH_3), 100.9 (CH), 102.4 (CH), 112.2 (CH), 112.9 (CH), 128.2 (C), 131.6 (C), 137.3 (C), 154.4 (C) ppm. MS (IS): m/z = 231.0 $[M + H]^+$. HRMS (ESI): calcd. for $C_{14}H_{19}N_2O$ $[M + H]^+$ 231.1491; found 231.1492.

(*S*)-2-(Furan-2-yl)piperidine (1c): Yield 26 mg, 69% as a colorless oil. R_f = 0.2 (acetone/MeOH, 9:1). $[\alpha]_D^{20}$ = –4.1 (c = 0.73, $CHCl_3$). IR (diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3302 (NH), 2970 (CH), 2903 (CH), 1396 (C=C) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45–

1.95 (m, 6 H, CH_2), 2.78–2.86 (m, 1 H, CH_2), 3.17–3.24 (m, 1 H, CH_2), 3.89–3.94 (m, 1 H, NCH), 3.97 (br. s, 1 H, NH), 6.28–6.35 (m, 2 H, ArH), 7.35–7.40 (m, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.6 (CH_2), 24.5 (CH_2), 29.6 (CH_2), 45.8 (CH_2), 53.9 (CH), 106.1 (CH), 110.3 (CH), 141.9 (CH), 154.7 (C) ppm. HRMS (ESI): calcd. for $C_9H_{14}NO$ $[M + H]^+$ 152.1072; found 152.1069.

(*S*)-2-Azepan-2-yl-5-methoxy-1*H*-indole (2b): Yield 50 mg, 82% as a yellow film. R_f = 0.13 (acetone/MeOH, 9:1). $[\alpha]_D^{20}$ = –25.7 (c = 0.15, $CHCl_3$). IR (diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3233 (NH), 2925 (CH), 2854 (CH), 1588 (C=C), 1487 (C=C), 1456 (C=C) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.66–1.91 (m, 5 H, 2×CH_2 and NH), 2.17–2.27 (m, 4 H, 2×CH_2), 2.95–3.01 (m, 2 H, CH_2), 3.80 (s, 3 H, OCH_3), 4.27 (d, J = 4.7 Hz, 1 H, CH), 6.34 (s, 1 H, ArH), 6.79 (dd, J = 8.8, 2.4 Hz, 1 H, ArH), 6.96 (d, J = 2.3 Hz, 1 H, ArH), (d, J = 8.7 Hz, 1 H, ArH), 9.75 (br. s, 1 H, NH) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 27.2 (CH_2), 27.5 (CH_2), 33.1 (CH_2), 45.4 (CH_2), 56.0 (CH_2), 56.3 (OCH_3), 63.1 (CH), 100.8 (CH), 102.3 (CH), 112.2 (CH), 112.7 (CH), 127.2 (C), 133.1 (C), 138.1 (C), 155.7 (C) ppm. MS (IS): m/z = 245.0 $[M + H]^+$. HRMS (ESI): calcd. for $C_{15}H_{21}N_2O$ $[M + H]^+$ 245.1648; found 245.1652.

(*S*)-2-(Dibenzo[*b*,*d*]furan-4-yl)azepane (2d): Yield 52 mg, 79% as a colorless oil. R_f = 0.21 (acetone/MeOH, 9:1). $[\alpha]_D^{20}$ = –18.9 (c = 0.26, $CHCl_3$). IR (diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3308 (NH), 2978 (CH), 2901 (CH), 1404 (C=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.63–1.93 (m, 6 H, CH_2), 2.03–2.14 (m, 2 H, CH_2), 2.98–3.06 (m, 1 H, CH_2), 3.21–3.29 (m, 1 H, CH_2), 4.37 (br. s, 1 H, NH), 4.49–4.53 (m, 1 H, NCH), 7.27–7.36 (m, 2 H, ArH), 7.43–7.48 (t, J = 7.5 Hz, 1 H, ArH), 7.53–7.60 (m, 2 H, ArH), 7.81–7.83 (d, J = 6 Hz, 1 H, ArH), 7.92–7.94 (d, J = 6 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.3 (CH_2), 26.7 (CH_2), 29.6 (CH_2), 36.4 (CH_2), 47.7 (CH_2), 58.2 (CH), 111.7 (CH), 119.4 (CH), 120.7 (CH), 122.7 (CH), 123.1 (CH), 124.2 (C), 124.3 (C), 124.6 (CH), 125.5 (C), 127.1 (CH), 153.0 (C), 155.9 (C) ppm. HRMS (ESI): calcd. for $C_{18}H_{20}NO$ $[M + H]^+$ 266.1542; found 266.1549.

General Procedure for Synthesis of Heterocyclic Boronate 11: Intermediate vinyl phosphate **9** (916 mg, 2 mmol) was dissolved in anhydrous dimethylformamide (20 mL) in a two-necked flask under a nitrogen atmosphere. To the solution were added, in the following order, bis(pinacolato)diboron (762 mg, 3 mmol), $(Ph_3P)_2PdCl_2$ (42 mg, 0.06 mmol), Ph_3P (32 mg, 0.12 mmol), and $Ba(OH)_2$ (513 mg, 3 mmol). The mixture was heated with an oil bath to 90 °C and left whilst stirring for 5 h, after which time the reaction was complete (by TLC). After cooling to room temperature, the mixture was diluted with Et_2O (60 mL) and washed with water (3×40 mL). The organic phase was dried with $MgSO_4$, filtered, and concentrated to give boronate **11** (672 mg) as a yellow oil, which was used in the next step without further purification.

Synthesis of Enehydrazide 5e: $Pd(OAc)_2$ (45 mg, 0.2 mmol), Ph_3P (105 mg, 0.4 mmol), and the crude boronate **11** (672 mg, 2 mmol) were dissolved in anhydrous dioxane (15 mL) in a Schlenk flask under a nitrogen atmosphere. To the solution was added 3-bromopyridine (474 mg, 3 mmol), followed by K_3PO_4, H_2O (921 mg, 4 mmol), and the resulting mixture was heated at 100 °C. After 4 h, the reaction was complete (by TLC) and the mixture was diluted with Et_2O (15 mL) and washed with water (20 mL). The organic phase was dried with Na_2SO_4, filtered, and concentrated. The crude oil was purified by column chromatography with acetone/petroleum ether (6:4) as eluent, to afford pure **5e** (321 mg, 56%) as a white solid.

(*S*)-1-[2-(Methoxymethyl)pyrrolidin-1-yl]-6-(pyridin-3-yl)-3,4-dihydropyridin-2(1*H*)-one (5e): Yield 321 mg, 56% as a white solid, m.p. 126–127 °C. R_f = 0.70 (acetone/PE, 6:4). $[\alpha]_D^{20}$ = –116.7 (c = 0.37, $CHCl_3$). IR (diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2890 (CH), 1674 (C=O), 1350 (C=C), 1103 (C–O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.21–1.31 (m, 1 H, CH_2), 1.46–1.57 (m, 1 H, CH_2), 1.90–2.05 (m, 2 H, CH_2), 2.24–2.73 (m, 4 H, CH_2), 2.87–3.05 (m, 3 H), 3.18 (s, 3 H), 3.48–3.55 (q, J = 7 Hz, 1 H), 3.76–3.84 (m, 1 H), 5.22–5.25 (m, 1 H, CH=), 7.24–7.28 (m, 1 H, ArH), 7.60–7.64 (m, 1 H, ArH), 8.52–8.55 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.8 (CH_2), 22.9 (CH_2), 27.9 (CH_2), 33.8 (CH_2), 52.1 (CH_2), 58.7 (CH_3O), 60.7 (CH), 76.0 (CH_2), 108.4 (CH), 122.3 (CH), 133.2 (C), 135.3 (CH), 143.6 (C), 148.6 (CH), 148.9 (CH), 169.4 (CO) ppm. HRMS (ESI): calcd. for $C_{16}H_{22}N_3O_2$ $[M + H]^+$ 288.1703; found 288.1700.

Synthesis of Cyclic Hydrazide 3e: A suspension of compound **5e** (100 mg, 0.35 mmol) in MeOH (10 mL) was stirred with activated Pd/C (10%, 20 mg) and a solution of HCO_2NH_4 (220 mg, 3.5 mmol) in distilled water (2 mL) was then added. The reaction mixture was heated to reflux for 5 h, filtered through Celite™ and diluted with water. Extraction with CH_2Cl_2 (3× 20 mL), drying over $MgSO_4$ and concentration under vacuum left an oily product, which was purified by chromatography on silica gel with acetone/petroleum ether (5:5) as eluent to give **3e** (78 mg, 77%) as a colorless oil.

(*S*)-1-[(*S*)-2-(Methoxymethyl)pyrrolidin-1-yl]-6-(pyridin-3-yl)piperidin-2-one (3e): Yield 78 mg, 77% as a colorless oil. R_f = 0.52 (acetone/PE, 5:5). $[\alpha]_D^{20}$ = –32.1(c = 1.08, $CHCl_3$). IR (diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2877 (CH), 1651 (C=O), 1396 (C=C), 1097 (C–O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.49–1.95 (m, 6 H, CH_2), 2.04–2.63 (m, 6 H, CH_2), 2.99–3.16 (m, 5 H), 3.63 (br. s, 1 H), 4.71–4.74 (t, J = 4.5 Hz, 1 H, NCH), 7.28–7.34 (m, 1 H, ArH), 7.58–7.62 (m, 1 H, ArH), 8.54–8.58 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.1 (CH_2), 23.3 (CH_2), 27.6 (CH_2), 31.9 (CH_2), 33.6 (CH_2), 50.9 (CH_2), 58.6 (CH_3O), 60.6 (CH), 60.7 (CH), 75.4 (CH_2), 123.1 (CH), 134.9 (CH), 138.1 (C), 148.8 (CH), 149.2 (CH), 169.7 (CO) ppm. HRMS (ESI): calcd. for $C_{16}H_{24}N_3O_2$ $[M + H]^+$ 290.1859; found 290.1865.

Synthesis of (*S*)-Anabasine (1e): A solution of borane–THF complex (1.0 M solution in THF, 5 mL, 5 mmol) was added at 0 °C to a stirred solution of **3e** (72 mg, 0.25 mmol) in THF (10 mL). The solution was stirred at room temperature for 15 min and then heated to reflux for 24 h. After the mixture was cooled in an ice-bath, 10% aqueous NaOH (10 mL) was added and the mixture was briefly stirred (5 min). The mixture was extracted with Et_2O (3×10 mL). The combined extracts were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel with CH_2Cl_2/MeOH (3:1) as eluent to give (*S*)-anabasine **1e**.

(*S*)-3-(Piperidin-2-yl)pyridine (1e): Yield 26 mg, 64% as a yellow oil. R_f = 0.23 (CH_2Cl_2/MeOH, 3:1). $[\alpha]_D^{20}$ = –79.2 (c = 0.8, MeOH); ref.[23b] $[\alpha]_D^{20}$ = –80 (c = 0.91, MeOH). Analytical and spectroscopic data were in agreement with those reported for the natural product.[23b]

Supporting Information (see footnote on the first page of this article): Copies of ^1H NMR and ^{13}C NMR spectra for all new compounds.

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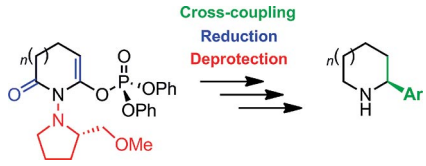
Cyclic Amines

An asymmetric synthesis of a variety of 2-heteroaryl cyclic amines through a (*S*)-aminomethylprolinol chiral pool strategy is described. This route was applied for the total synthesis of (–)-anabasine.



Keywords: Synthetic methods / Asymmetric synthesis / Chiral auxiliaries / Cross-coupling / Amines

