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The Asymmetric Synthesis of 1-Alkyl-2,3,4,5-Tetrahydro-Benzazepines and Benzo[β]-1-Azabicyclo[5,3,1]Decanes†

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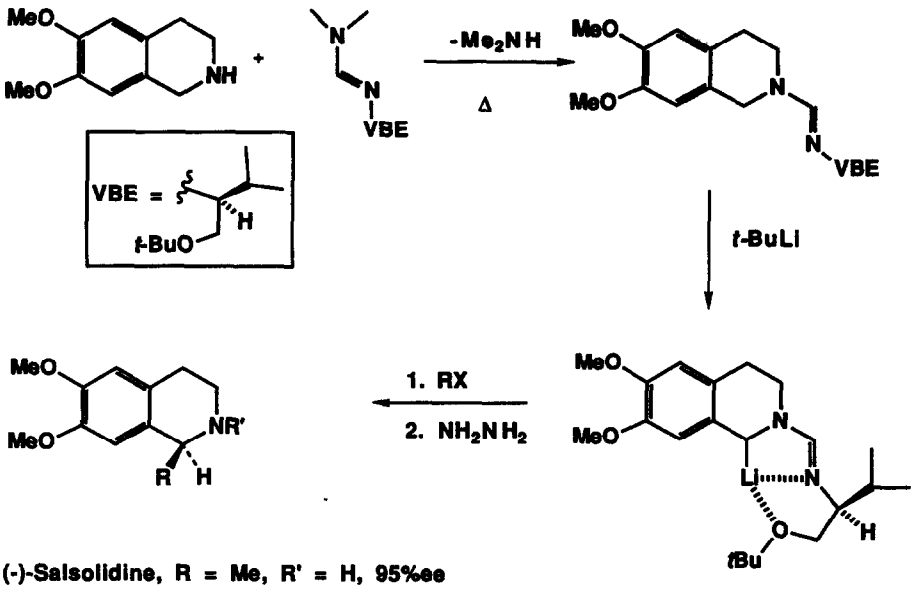
Abstract: *The metalation-alkylation of benzazepine formamidines gives high yields and good diastereoselectivity of 1-substituted derivatives. Removal of the chiral auxiliary leads to the title compounds in 84-96% ee and represents the first chiral benzazepines prepared via asymmetric synthesis.*

1-Aryl and 1-alkyl 2-benzazepines continue to generate considerable interest as a result of their pharmacological properties. Compounds in this class have been found to be potent platelet antiaggregatory drugs, CNS agents, and specific ligands for seritonin and dopamine receptor subtypes.[1] The 1-alkyl-2-benzazepine nucleus is also found in a number of the *Cephalotaxus* alkaloids.[2] Although these compounds have been synthesized by a variety of methods, no asymmetric synthesis has been reported. Previous work in this group has demonstrated that chiral formamidines can be used to synthesize a wide variety of isoquinoline alkaloids in good yields and with very high selectivity (Scheme 1).[3] This methodology has now been extended, in a preliminary study, to the synthesis of chiral 1-alkyl-2,3,4,5-tetrahydro-1-H-2-benzazepines.

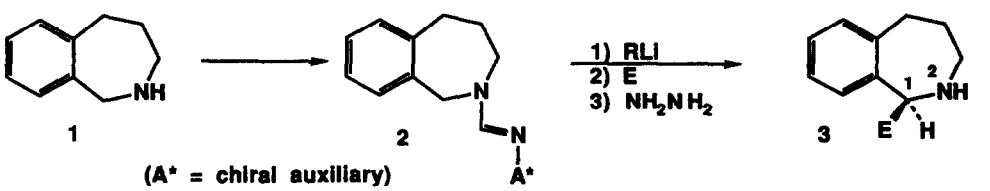
†This paper is dedicated to Professor Shun-ichi Yamada on the occasion of his 77th birthday, and with gratitude for his many contributions in organic chemistry.



(-)-Salsolidine, R = Me, R' = H, 95%ee
(+)-Laudanosine, R = 3,4-(MeO)$_2$PhCH2, R' = Me, 96% optical purity

Scheme 1

The primary goal of this work was to determine the selectivity obtained in the alkylation of the chiral formamidine **2** (Scheme 2). Although work in the isoquinoline series suggests that these reactions should be stereoselective, it was unclear how the less rigid 7-membered ring would effect the extent of asymmetric induction. Thus, we set out to make the appropriate formamidines.

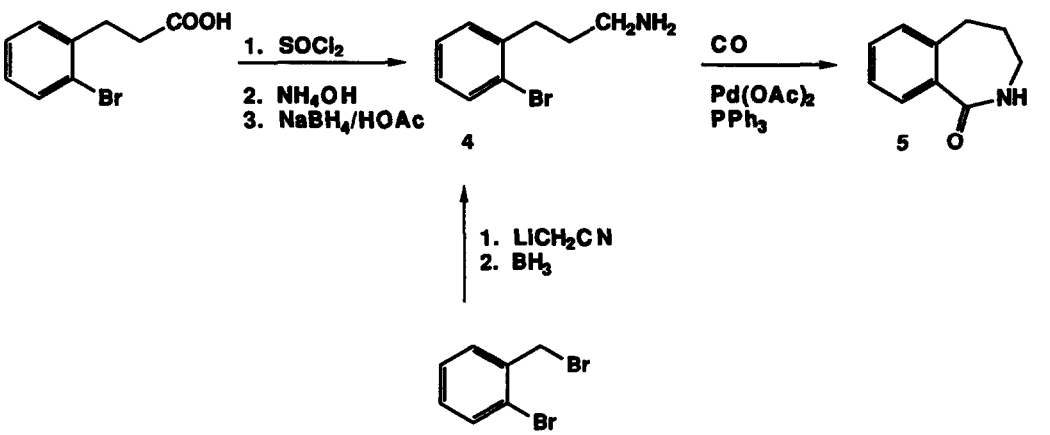


(A* = chiral auxiliary)

Scheme 2

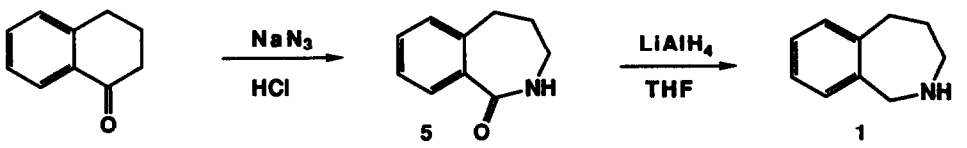
A variety of methods have been reported for the synthesis of substituted 2-benzazepines, however, suprisingly few of these methods yield the simple benzazepine **1**.[4,1b] Attempts to synthesize **1** by the classic Bischler-Napieralski cyclization were unsuccessful.[5] An examination of the literature repeatedly revealed that the cyclization is quite sensitive to substitution on the aromatic ring. Thus, while Bischler-Napieralski type cyclizations have been reported for electron rich systems it is apparent that this method is not productive for unactivated aromatic precursors.[6]

We next investigated the palladium catalyzed amidation reaction reported by Ban (Scheme 3).[7] Synthesis of the pivotal brominated amine **4** was accomplished by the alkylation of lithiated acetonitrile with 2-bromobenzyl bromide followed by borane reduction. This "one pot" method gave a moderate yield of the amine **4** (50%) and was more efficient than the synthesis from 3-(2-bromophenyl)-propionic acid. Unfortunately, the palladium catalyzed carbonylation/cyclization of **4** provided a complex mixture of products from which isolation of the amide **5** (30%) was exceedingly difficult.



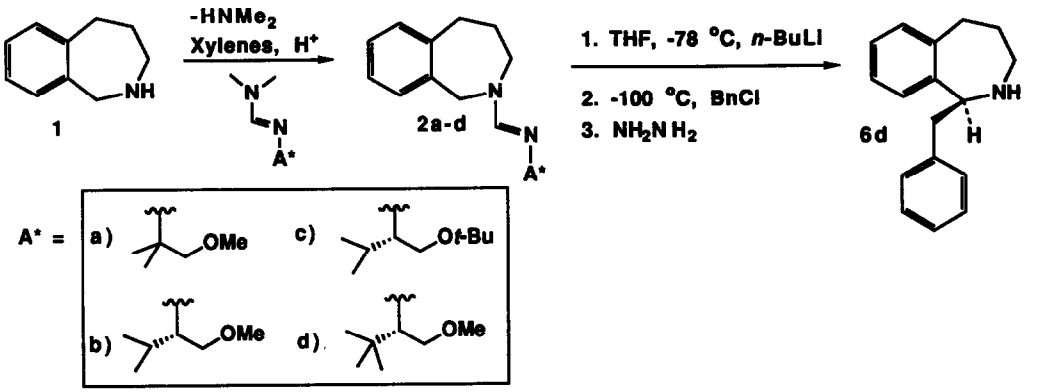
Scheme 3

The desired amide **5** could be obtained simply and in moderate yields (42%) by modification of the Schmidt reaction previously reported by Hjelte and Agback (Scheme 4).[8] Thus, addition of sodium azide to an ice cold solution of α-tetralone in HCl and warming, after 30 minutes, to ambient temperature provided a mixture of 2-benzazepine-1-one and 1-benzazepine-2-one. Silica gel chromatography (benzene/methanol 2:1) and recrystallization from hexane/ethyl acetate provided the pure amide **5**. Reduction with lithium aluminum hydride in THF yields the benzazepine **1** (81%).



Scheme 4

The formamidines **2a-d** were readily obtained by an exchange reaction with the corresponding *N,N*-dimethyl formamidines (Scheme 5).[9] The exchange proved to be sluggish in refluxing toluene (4-6 d), but was virtually complete after 24 hours in refluxing xylenes. The formamidines **2a-d** could be purified by silica gel chromatography; however, better yields were obtained by distillation at reduced pressure.



Scheme 5

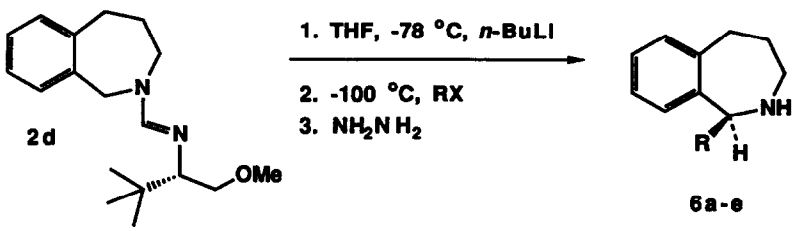
Alkylation of chiral formamidines **2b-d** with benzyl chloride at -100 °C and subsequent hydrazinolysis gave the corresponding free amine **6d** in moderate to good yields with excellent selectivity (Table 1). The (L)-valinol-*t*-butyl-ether **2c** and the (L)-*tert*-leucinol-methyl-ether **2d** were only slightly more selective than the (L)-valinol-methyl-ether **2b**. The absolute configuration of the major isomer (*S*) in each case has been tentatively assigned based on earlier precedents.[3] The assignment of absolute stereochemistry by X-ray crystalography is in progress.

Table1. Alkylation of formamidine **2a-d** with Benzyl chloride.

Formamidine	Yield (%)	Ratio[a] (S:R)
2a (achiral)	87	1:1
2b	60	92:8
2c	78	94:6
2d	82	95:5

a) Ratios were determined by chiral HPLC of **6d** using a Chiracel OD column.

The (S)-leucine-methyl ether formamidine **2d** was then alkylated with a variety of simple electrophiles (Scheme 6). After hydrazinolysis the corresponding amines were obtained in good yield and with excellent selectivity (84-96% ee, Table 2). It was found that alkyl iodides and bromides reacted at a moderate rate (3-6 h) while the alkyl chlorides were prohibitively slow (18-24 h).



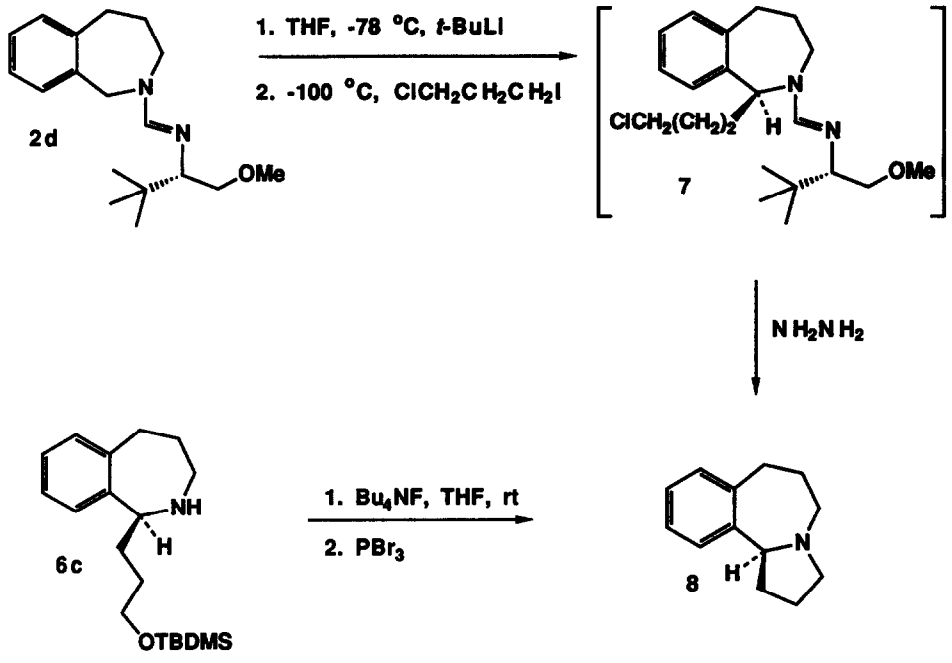
Scheme 6

Table 2. Alkylation of (S)-*N'*-(Leucinol-methyl-ether)-2,3,4,5-tetrahydro-1H-2-benzazepine Formamidine **2d**.

Entry	Electrophile (RX)	yield (%) **6**	Ratio[a] (S:R) **6**
6a	CH_3I	59	94:6
6b	$CH_3CH_2CH_2Br$	74	92:8
6c	$TBSOCH_2CH_2CH_2I$	70	98:2
6d	BnCl	82	95:5
6e	3-MeO-BnCl	57	96:4

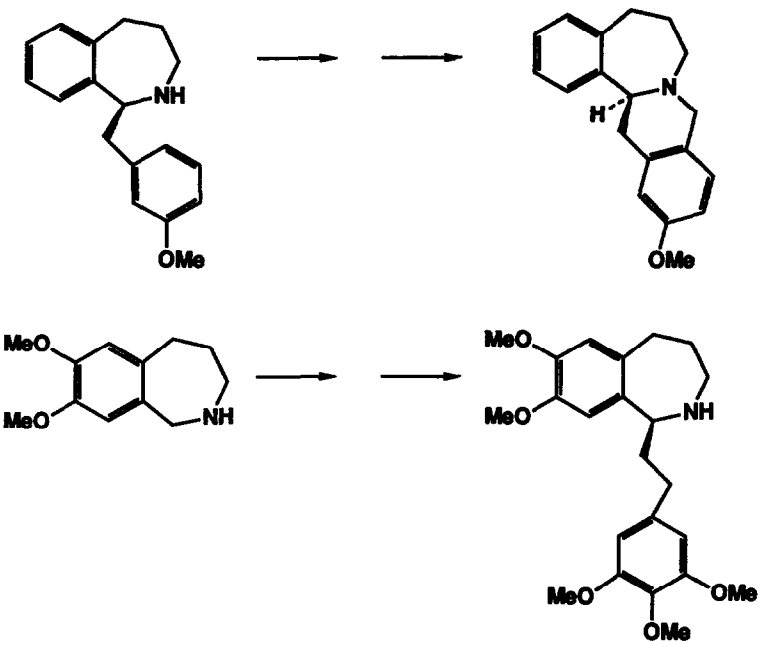
a) Ratios were determined by chiral HPLC of **6a-6e** or the corresponding napthamide using a Chiracel OD column.

Alkylation of the formamidine **2d** with 1-chloro-3-iodopropane gave the intermediate formamidine **7** which spontaneously cyclized to the tricyclic amine **8** on hydrazinolysis (Scheme 7). Although the amine **8** was optically active ($[\alpha]_D$ = + 14.5) it was not possible to determine the extent of asymmetric induction by chiral HPLC or ^1H NMR (chiral shift reagents). An optical purity of > 90% was determined, however, by comparison to the rotation of amine **8** generated by elaboration of the TBDMS ether **6c** (96 % ee, $[\alpha]_D$ = + 15.2).



Scheme 7

Thus, 2,3,4,5-tetrahydro-1H-2-benzazepines **2** can be alkylated in good yield and with good selectivity. The results of this study suggest that the less rigid cycloheptyl ring has little effect on the extent of asymmetric induction. The starting amine **1** could be readily obtained via the Schmidt reaction of α-tetralone. Tentative assignment of the absolute stereochemistry for the major isomer (*S*) was made based on past precedent, and will be confirmed by X-ray crystallography. This methodology is currently being extended to include the synthesis of



Scheme 8

EXPERIMENTAL

General ^{1}H NMR spectra were recorded at 300 MHz (Bruker AC-300). ^{13}C NMR spectra were recorded at 75.5 MHz. Chemical shifts for proton and carbon resonances are reported in ppm (δ) relative to *deuterio*-benzene or *deuterio*-chloroform (δ = 7.15 or 7.24, respectively) and (δ = 128.0 or 77.0 respectively). Optical rotations were determined using a Rudolph Research Autopol III automatic polarimeter (598 nm) at ~ 22 °C. Fourier Transformed Infrared (IR) spectra were recorded on a Perkin Elmer 1600 spectrophotometer. Low resolution mass spectra were obtained with a Hewlett Packard 5970 series mass selective detector (ionization potential 70 eV) in conjunction with a Hewlett Packard Series II capiliary gas chromatograph. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, Georgia. Melting points are reported uncorrected as recorded on a MEL-TEMP capillary chambered apparatus.

Chromatography: Thin-Layer chromatography (TLC) was performed on Kieselgel 60 F254 aluminum plates (0.20 mm) precoated with silica gel. Reaction components were visualized by UV (254 nm), Iodine, ninhydrin, or Dragondorf's solution. Silica gel (60 A) for flash chromatography was purchased from Amicon (200-450 mesh).

Materials: Unless otherwise indicated, all reagents were obtained from commercial suppliers and were used without further purification. Solvents were dried according to established protocols by distillation under argon from an appropriate drying agent. Thus, tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl. Pentane was distilled from lithium aluminum hydride. Benzene, toluene, and dichloromethane (CH_2Cl_2) were distilled from calcium hydride. *N,N*-Dimethyl formamide was distilled from calcium hydride under reduced pressure (< 20 torr), and triethylamine (TEA) was stored over KOH. Reactions involving air and/or moisture sensitive reagents were conducted under an atmosphere of argon, and the glassware was oven-dried (120 °C) evacuated and purged with argon. Alkyl halides were typically passed through a short column (5 X 50 mm) of basic alumina (Aldrich, Activated Basic aluminum oxide, Brockmann I, 150 mesh) prior to use.

2,3,4,5-Tetrahydro-1H-2-benzazepine-1-one 5. Sodium azide (2.7g, 41.8 mmol) was added in portions to an ice cold solution of freshly distilled α-tetralone (6.1g, 41.8 mmol) in concd HCl (75 mL). The resulting mixture was allowed to stir at 0 °C for 30 min and then was allowed to warm to rt while stirring overnight. The reaction mixture was poured into ice-water (300 mL), made basic (pH 9) with solid K_2CO_3, and extracted (3x40 mL) with CH_2Cl_2. The organic layers were combined, dried (Na_2SO_4), and concentrated to give the crude amide. Kugelrohr distillation (150 °C, 1mm), silica gel chromatography (benzene/ethyl acetate 1:2), and recrystalization from ethyl acetate/hexane (1:3) provided 2.86 g (42%) of the amide as a white solid: mp 101 °C (Lit. mp 100-104.5 °C)[7], ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 1.6, 7.4 Hz, 1H), 7.2-7.4 (m, 3H), 7.16 (dd, *J* = 1.0, 7.2 Hz, 1H), 3.10 (q, *J* = 6.3 Hz, 2H), 2.83 (t, *J* = 7.2 Hz, 2H), 1.99 (quintet, *J* = 6.8, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.1 (s), 138.3 (s), 134.9 (s), 131.2 (d), 128.6 (d), 128.5 (d), 126.9 (d), 39.5 (t), 30.5 (t), 30.2 (t); IR (CCl_4) 3207, 3068, 2947, 1657, 1605, 1466, 1397, 1364, 1337, 908 cm^{-1}. Low resolution mass spectrum (gc-ms) *m/e* (rel abundance) 161 (M^+, 100), 132 (59), 132 (28), 131 (56), 104 (44). **Anal.** Calcd for $C_{10}H_{11}N$ O: C, 74.50, H, 6.87, N, 8.68. Found: C, 74.58, H, 6.91, N, 8.69.

1,2,3,4-Tetrahydro-1H-2-benzazepine 1. The amide **5** (2.5 g, 15.5 mmol) was dissolved in THF (20 mL) and carefully added to a slurry of lithium aluminum hydride (2.0 g, 54 mmol) in THF (75 mL) at 0 °C. The resulting mixture was heated to reflux for 24 h, cooled to rt and quenched with a minimum of 20% KOH. The salts were removed by filtration, the organic layer was dried (Na_2SO_4), and concentrated to a light oil. Kugelrohr distillation (120 °C, 1.0 mm) provided 1.84 g of the amine as a colorless liquid (81 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.0-7.13 (m, 4H), 3.91 (s, 2H), 3.19 (apparent t, *J* = 5.8Hz, 2H), 2.92 (m, 2H), 1.65-1.75 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 142.8 (s), 142.6 (s), 129.1 (d), 128.3 (d), 127.0 (d), 126.0 (d), 55.0 (t), 53.5 (t), 36.1 (t), 30.8 (t); IR (thin film) 3100-3500 br, 3061, 3017, 2925, 2842, 1493, 1455, 1298, 1133, 1099, 880, 849 cm^{-1}.

Low resolution mass spectrum (gc-ms) *m/e* (rel abundance) 147 (M^+,100), 146 (57), 132 (28), 117 (75). The hydrochloride salt was made by passing dry HCl through an ether solution of the free amine. Recrystalization from methanol/ether gave the salt as a colorless solid: mp 225 °C (Lit. mp 223-225 °C).[8] **Anal.** Calcd for $C_{10}H_{14}NCl$: C, 65.39, H, 7.68, N, 7.62. Found: C, 65.28, H, 7.74, N, 7.60.

General Procedure for Formamidine Exchange Reactions to 2

In an oven-dried round-bottomed flask equipped with a stir bar and a condenser (capped with a septum) was placed the appropriate *N,N*-dimethyl formamidine, a catalytic amount (1 drop) of acetic acid, and 0.9 equivalents of the benzazepine in dry xylenes. Through the septum was passed, via needle, a gentle stream of argon which was allowed to exit through a second needle. The solution was heated to reflux until the evolution of dimethylamine was no longer detected (dimethylamine was detected by holding moist pH paper over the exit needle). The xylenes were removed *in vacuo* and the product was purified by bulb-to-bulb distillation or flash chromatography.

***N'*-(1-Methoxy-2-methyl-2-propyl)-2,3,4,5-tetrahydro-1H-2-benzazepine Formamidine 2a.** According to the general procedure for the exchange reaction benzazepine **1** (1.2 g, 8.2 mmol) was combined with *N,N*-dimethyl-*N'*-(1-methoxy-2-methyl-2-propyl) formamidine[9a] (1.36 g, 8.6 mmol). Kugelrohr distillation (220 °C, 0.2 mm) provided 2.1g (98%) of the formamidine **2a** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.1-7.35 (m, 5H), 4.41 (br s, 2H), 3.58 (apparent t, J = 2.1 Hz, 2H), 3.24 (s, 3H), 3.10 (s, 2H), 2.92 (m, 2H), 1.75 (m, 2H), 1.07 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.8 (d), 141.5 (s), 139.2 (s), 129.0 (d), 127.1 (d), 125.8 (d), 82.7 (t), 59.2 (q), 56.0 (s), 52.4 (t), 51.1 (t), 34.8 (t), 28.4 (t), 25.8 (q); IR (thin film) 3018, 2964, 2927, 1643, 1147, 1109, 754 cm^{-1}. Low resolution mass spectrum (gc-ms) *m/e* (rel abundance) 260 (M^+, 8), 215 (100), 146 (65).

(S)-*N'*-(Valinol-methyl-ether)-2,3,4,5-tetrahydro-1H-2-benzazepine Formamidine 2b. According to the general procedure for the exchange reaction benzazepine **1** (557 mg, 3.78 mmol) was combined with *N,N*-dimethyl-*N'*-(valinol-methyl-ether) formamidine[9b] (684 mg, 3.98 mmol). Purification by silica gel chromatography (hexane/ethyl acetate/TEA 16:3:1) provided 416 mg (40%) of the formamidine **2b** as a yellow oil: $[\alpha]_D$ = +8.36 (c = 7.1, $CHCl_3$),^{1}H NMR (300 MHz, C_6D_6) δ 7.0-7.3 (m, 5H), 4.54 (br d, J = 14.7 Hz, 1H), 4.27 (d, J = 14.7 Hz, 1H), 3.35-3.75 (m, 2H, partially obscured by dd at 3.43), 3.43 (dd, J = 4.5, 9.6 Hz, 1H), 3.22 (s, 3H), 3.21 (t, J = 7.2 Hz, 1H, partially obscured by s at 3.22), 2.8-3.0 (m, 2H), 2.71 (dt, J = 4.8, 7.8 Hz, 1H), 1.55-1.85 (m, 3H), 0.74 (d, J = 6.7 Hz), 0.66 (d, J = 6.7 Hz), ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 152.6 (d), 141.4 (s), 139.1 (s), 129.1 (d), 127.1 (d), 125.7 (d), 76.2 (t), 70.9 (d), 58.8 (q), 52.6 (t), 51.7 (t), 34.9 (t), 30.5 (d), 28.4

(t), 19.9 (t), 17.8 (t); IR (thin film) 3019, 2929, 1651, 1492, 1454, 1384, 1163, 1113, 1080, 955 cm^{-1} Low resolution mass spectrum (gc-ms) *m/e* (rel abundance) 274 (M^+, 18), 229 (70), 146 (100).

(*S*)-*N'*-(Valinol-*t*-butyl-ether)-2,3,4,5-tetrahydro-1H-2-benzazepine Formamidine 2c. According to the general procedure for the exchange reaction benzazepine **1** (540 mg, 3.7 mmol) was combined with *N,N*-dimethyl-*N'*-(valinol-t-butyl-ether) formamidine[9b] (800 mg, 3.7 mmol). Purification by silica gel chromatography (hexane/ethyl acetate/TEA 16:3:1) provided 814 mg (70%) of the formamidine as a yellow oil: $[\alpha]_D$ = + 13.7 (c = 1.7, $CHCl_3$),^1H NMR (300 MHz, $CDCl_3$) δ 7.0-7.2 (m, 5H), 4.39 (AB q, J_{AB} = 14.8 Hz, 2H), 3.45-3.7 (m, 2H), 3.41 (dd, *J* = 8.8, 5.1 Hz, 1H), 3.06 (apparent t, *J* = 8.0 Hz, 1H), 2.8-3.0 (m, 2H), 2.64 (dt, *J* = 5.2, 7.2 Hz, 1H), 1.65-1.85 (m, 3H), 1.01 (s, 9H), 0.78 (d, *J* = 6.8 Hz), 0.68 (d, *J* = 6.8 Hz), ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 152.6 (d), 141.4 (s), 139.1 (s), 129.1 (d), 127.1 (d), 125.7 (d), 72.2 (s), 71.0 (d), 64.9 (t), 53.0 (t), 51.4 (t), 35.0 (t), 30.1 (d), 28.2 (t), 27.5 (q), 20.1 (q), 17.6 (q); IR (thin film) 3019, 2970, 1650, 1454, 1384, 1197, 1097 cm^{-1} Low resolution mass spectrum (gc-ms) *m/e* (rel abundance) 316 (M^+, 18), 229 (100), 146 (93).

(S)-*N'*-(Leucinol-methyl-ether)-2,3,4,5-tetrahydro-1H-2-benzazepine Formamidine 2d. According to the general procedure for the exchange reaction benzazepine **1** (1.19 g, 8.0 mmol) was combined with *N,N*-dimethyl-*N'*-(leucinol-methyl-ether) formamidine[9c] (1.52 g, 8.2 mmol). Kugelrohr distillation (240 °C, 0.2 mm) provided 1.8 g (81%) of the formamidine as a clear oil: $[\alpha]_D$ = + 49.2 (c = 6.0, EtOH),^1H NMR (300 MHz, $CDCl_3$) δ 7.2-73 (m, 1H), 7.16 (s, 1H), 7.0-7.1 (m, 3H), 4.61 (br d, *J* = 14.6 Hz, 1H), 4.25 (d, *J* = 14.6 Hz, 1H), 3.52-3.58 (m, 3H), 3.19 (s, 3H), 3.18 (t, *J* = 8.9 Hz, 1H, partially obscured by s at 3.19), 2.8-3.0 (m, 2H), 2.55 (dd, *J* = 2.8, 8.7 Hz, 1H), 1.6-1.8 (m, 2H), 0.72 (s, 9H),^{13}C NMR (75.5 MHz, $CDCl_3$) δ 152.1 (d), 141.4 (s), 139.4 (s), 129.5 (d), 128.9 (d), 126.9 (d), 125.5 (d), 74.5 (t), 74.5 (d), 58.7 (q), 52.4 (t), 35.1 (t), 33.4 (s), 28.8 (t), 26.8 (q); IR (thin film) 3019, 2947, 1651, 1453, 1391, 1359, 1161, 1120, 1101, 955 cm^{-1} Low resolution mass spectrum (gc-ms) *m/e* (rel abundance) 288 (M^+, 15), 243 (72), 231 (56), 146 (100).

General Procedure for Alkylation and Hydrazinolysis of Formamidines

An oven-dried round-bottomed flask was evacuated and purged (3X) with argon. The formamidine was introduced and the flask was pumped under high vacuum (1 mm) while carefully heating with a hot air gun. After cooling under argon sufficient THF was added to give a 0.02 M solution. The resulting solution was cooled to -78 °C (dry ice/acetone) and treated with the appropriate base (1.2 equivalents) to give the corresponding anion (yellow-orange). After stirring for 30 min at -78 °C the flask was transfered to a -98 °C bath (methanol/liq N_2) and the electrophile (1.2 equivalents) was added dropwise *via* syringe. The resulting solution was maintained at

-98 °C until the reaction was complete (disappearance of color) then warmed to -78 °C and quenched with methanol. After warming to rt the volatiles were removed *in vacuo*. The resulting oil was taken up in 8 mL ethanol and 1 mL of glacial acetic acid, cooled to 0 °C, and treated with 2 mL of hydrazine monohydrate. The resulting mixture was stirred at ambient temperature overnight. The volatiles were removed *in vacuo* and the residue was partitioned between ethyl acetate and aqueous sodium bicarbonate (20 %). The aqueous layer was extracted (3X) with ethyl acetate, the organic layers were combined, dried (Na_2SO_4), and concentrated to give the crude amine which was purified by silica gel chromatography.

(±)1-Benzyl-2,3,4,5-tetrahydro-1H-2-benzazepine 6d from 2a. According to the general alkylation procedure formamidine **2a** (300 mg, 1.15 mmol) was treated with *n*-butyllithium (830 µL, 1.5 mmol, 1.8 M in hexane) and benzyl chloride (159 µL, 1.38 mmol) to give after hydrazinolysis and silica gel chromatography (hexane/ethyl acetate/TEA 14:5:1) 283 mg (87%) of the amine as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) 7.4-7.4 (m, 9H), 4.18 (dd, J = 4.9, 10.0 Hz, 1H), 2.83-3.33 (m, 6H), 1.58-1.82 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 143.9 (s), 141.9 (s), 139.4 (s), 129.5 (d), 129.0 (d), 128.4 (d), 126.7 (d), 126.3 (d), 126.0 (d), 125.7 (d), 62.4 (d), 50.3 (t), 39.8 (t), 35.2 (t), 29.7 (t); IR (thin film) 3327, 3061, 3025, 2926, 2848, 1602, 1495, 1453, 1301, 1135, 1105, 1031cm^{-1}. Low resolution mass spectrum (gc-ms) *m/e* (rel abundance) 237 (M^+, 0.1), 146 (100), 117 (30), 91 (31). Treatment of the amine in CH_2Cl_2 with 1-napthoyl chloride and TEA provided after basic workup and recrystallization from hexane/ethyl acetate the napthamide: mp 148 °C, **Anal.** Calcd for $C_{28}H_{25}N$ O: C, 85.89, H, 6.43, N, 3.57. Found: C, 85.64, H, 6.48, N, 3.49.

1-Benzyl-2,3,4,5-tetrahydro-1H-2-benzazepine 6d from 2b. According to the general alkylation procedure, formamidine **2b** (200 mg, 0.729 mmol) was treated with *n*-butyllithium (486 µL, 0..876 mmol, 1.8 M) and benzyl chloride (100.8 µL, 0.876 mmol) to give after hydrazinolysis and silica gel chromatography (hexane/ethyl acetate/TEA 14:5:1) 104 mg (60%) of the amine as a colorless oil: $[\alpha]_D$ = -10.64 (c = 2.1, $CHCl_3$). All spectra were identical to that reported above.

1-Benzyl-2,3,4,5-tetrahydro-1H-2-benzazepine 6d from 2c. According to the general alkylation procedure, formamidine **2c** (300 mg, 0.95 mmol) was treated with *n*-butyllithium (1.0 mL, 1.14 mmol, 1.1 M) and benzyl chloride (131 µL, 1.14 mmol) to give after hydrazinolysis and silica gel chromatography (hexane/ethyl acetate/TEA 14:5:1) 176 mg (78%) of the amine as a colorless oil: $[\alpha]_D$ = -17.4 (c = 11.2, Bz). All spectra were identical to that reported above.

1-Benzyl-2,3,4,5-tetrahydro-1H-2-benzazepine 6d. According to the general alkylation procedure, formamidine **2d** (73 mg, 0.26 mmol) was treated with *n*-butyllithium (133 µL, 0.28 mmol, 2.13 M) and benzyl chloride (32.5 µL, 0.28 mmol) to give after hydrazinolysis and silica gel

chromatography (hexane/ethyl acetate/TEA 14:5:1) 50 mg (82%) of the amine as a colorless oil: $[\alpha]_D$ = -6.0 (c = 0.4, EtOH). All spectra were identical to that reported above.

1-Methyl-2,3,4,5-tetrahydro-1H-2-benzazepine 6a. According to the general alkylation procedure, formamidine **2d** (223 mg, 0.77 mmol) was treated with *n*-butyllithium (372 μL, 0.93 mmol, 2.5 M in hexane) and methyl iodide (57 μL, 0.93 mmol) to give after hydrazinolysis and silica gel chromatography (hexane/ethyl acetate/TEA 14:5:1) 74 mg (59%) of the amine **6a** as a light yellow oil: $[\alpha]_D$ = +13.3 (*c* = 9.0, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.1-7.3 (m,4H), 4.06 (q, *J* = 6.9 Hz, 1H), 3.32 (dt, *J* = 3.8, 13.5 Hz, 1H), 3.01-3.15 (m, 2H), 2.86 (ddd, *J* = 2.0, 7.4, 14.3 Hz, 1H), 1.7-1.8 (m, 1H), 1.47-1.60 (m, 2H), 1.51 (d, *J* = 6.9 Hz, 3H, partially obscured by multiplet), 1.43 (br s, 1H) ; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 145.4 (s), 142.2 (s), 129.3 (d), 126.6 (d), 125.9 (d), 124.5 (d), 55.6 (d), 51.3 (t), 35.5 (t), 29.9(t), 20.7 (q); IR (thin film) 3274, 3018, 2927, 1488, 1455, 1372, 1316, 1139, 1014, 848 cm^{-1}. Low resolution mass spectrum (gc-ms) *m/e* (rel abundance)161 (M^+, 14), 146 (100), 117 (21), 91 (10). The hydrochloride salt was prepared by passing dry HCl through an ether solution of the free amine. Recrystalization from methanol/ether provided the salt as a colorless solid: mp 211 °C. **Anal.** Calcd for $C_{11}H_{16}NCl$: C, 66.82, H, 8.15, N, 7.08. Found: C, 66.72, H, 8.12, N, 7.08.

1-Propyl-2,3,4,5-tetrahydro-1H-2-benzazepine 6b. According to the general alkylation procedure formamidine **2d** (250 mg, 0.87 mmol) was treated with *t*-butyllithium (530 μL, 0.95 mmol, 1.8 M in pentane) and 1-bromopropane (118 mg, 95 mmol) to give after hydrazinolysis and silica gel chromatography (hexane/ethyl acetate/TEA 17:2:1) 122 mg (74%) of the amine **6b** as a colorless oil: $[\alpha]_D$ = -29.40 (c = 3.4, benzene); ^{1}H NMR (300 MHz, C_6D_6) δ 7.0-7.5 (m,4H), 3.69 (apparent t, *J* = 7.1 Hz, 1H), 3.09 (dt, *J* = 4.6, 14.2 Hz, 1H), 2.7-2.9 (m, 3H), 1.3-1.7 (m, 6H), 0.94 (t, *J* = 6.4 Hz, 3H), 0.63 (br s, 1H); ^{13}C NMR (75.5 MHz, C_6D_6) δ 146.4 (s), 142.3 (s), 129.8 (d), 126.5 (d), 126.1 (d), 125.8 (d), 61.0 (d), 50.3 (t), 36.5 (t), 35.7 (t), 30.9 (t), 20.5 (t), 14.4 (q); IR (thin film) 3325, 3057, 3016, 2949, 2923, 2867, 1486, 1452, 1139, 1106, 742 cm^{-1}. Low resolution mass spectrum (gc-ms) *m/e* (rel abundance) 189 (M^+, 0.1), 146 (100), 130 (5), 117 (12). The hydrochloride salt was prepared by passing dry HCl through an ether solution of the free amine. Recrystalization from methanol/ether provided the salt as a colorless solid: mp 198 °C. **Anal.** Calcd for $C_{13}H_{20}NCl$: C, 69.16, H, 8.92, N, 6.20. Found: C, 68.94, H, 8.98, N, 6.16.

1-(3-*t*-Butyldimethylsiloxy)propyl-2,3,4,5-tetrahydro-1H-2-benzazepine 6c. According to the general alkylation procedure formamidine **2d** (290 mg, 1.0 mmol) was treated with *t*-butyllithium (667 μL, 1.2 mmol, 1.8 M in pentane) and 1-chloro-(3-*t*-butyldimethylsiloxy)propane (299 mg, 1.2 mmol) to give after hydrazinolysis and silica gel chromatography (hexane/ethyl acetate/TEA 17:2:1) 224 mg (70%) of the amine **6e** as a colorless oil: $[\alpha]_D$ = -21.67 (*c* = 2.6, benzene); ^{1}H NMR (300 MHz, C_6D_6) δ 7.0-7.2 (m, 4H), 3.74 (dd, *J* = 4.6,

8.7 Hz, 1H), 3.65 (t, J = 5.8 Hz, 2H), 3.13 (dt, J = 4.4, 14.1 Hz, 1H), 2.7-2.9 (m, 3H), 1.6-1.9 (m, 4H), 1.3-1.5 (m, 2H), 1.02 (s, 9H), 0.68 (br s, 1H), 0.11 (s, 6H) ; ^{13}C NMR (75.5 MHz, C_6D_6) δ 146.3 (s), 142.4 (s), 129.8 (d), 126.6 (d), 126.2 (d), 125.7 (d), 63.5 (t), 61.1 (d), 50.4 (t), 35.7 (t), 30.9 (t), 30.8 (t), 30.7 (t), 26.1 (q), 18.5 (s), -5.1 (q); IR (thin film) 3323, 3060, 3016, 2949, 2927, 2854, 1470, 1253, 1099, 834, 774, 746 cm^{-1}. Low resolution mass spectrum (gc-ms) *m/e* (rel abundance) 319 (M^+, 0.01), 146 (100), 101 (20), 75 (19).

1-(3-Methoxybenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine 6e. According to the general alkylation procedure formamidine **2d** (154 mg, 0.53 mmol) was treated with *n*-butyllithium (244 µL, 0.58 mmol, 2.41 M in hexane) and 3-methoxybenzyl chloride (Aldrich) (90.8 mg, 0.58 mmol) to give after hydrazinolysis and silica gel chromatography (hexane/ethyl acetate/TEA 15:4:1) 81 mg (57%) of the amine **6c** as a colorless oil: $[\alpha]_D$ = -8.76 (c = 16.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.1-7.3 (m, 5H), 6.7-6.9 (m, 3H), 4.16 (dd, J = 4.7, 10 Hz, 1H), 3.78 (s, 3H), 3.2-3.3 (m, 2H), 2.8-3.1 (m, 4H), 1.6-1.8 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.6 (s), 144.0 (s), 142.0 (s), 141.1 (s), 129.5 (d), 129.4 (d), 126.7 (d), 126.0 (d), 125.6 (d), 121.4 (d), 114.8 (d), 111.5 (d), 62.2 (d), 55.1 (q), 50.5 (t), 39.9 (t), 35.2 (t), 29.7 (t); IR (thin film) 3326, 3016, 2928, 2835, 1600, 1489, 1453, 1260, 1152, 1105, 1043, 936, 875 cm^{-1}. Low resolution mass spectrum (gc-ms) *m/e* (rel abundance) 267 (M^+, 0.06), 146 (100), 117 (10). The hydrochloride salt was prepared by passing dry HCl through an ether solution of the free amine. Recrystalization from methanol/ether provided the salt as a colorless solid mp 174 °C. **Anal.** Calcd for $C_{18}H_{22}NOCl$: C, 71.15, H, 7.29, N, 4.61. Found: C, 71.06, H, 7.33, N, 4.62.

Tricyclic amine 8. According to the general alkylation procedure, the formamidine **2d** (260 mg, 0.90 mmol) was treated with *t*-butyllithium (600 µL, 1.08 mmol, 1.8 M in pentane) and 3-chloro-1-iodopropane (Aldrich) (368 mg, 1.8 mmol) to give after hydrazinolysis and silica gel chromatography (hexane/ethyl acetate/TEA 17:2:1) 130 mg (77%) of the amine as a colorless oil: $[\alpha]_D$ = + 14.5 (c = 1.2, benzene); ^{1}H NMR (300 MHz, C_6D_6) δ 7.0-7.2 (m, 4H), 3.58 (t, J = 7.6, 1H), 3.0-3.1 (m, 2H), 2.7- 2.8 (m, 1H), 2.1-2.5 (m, 3H), 1.8-1.95 (m, 1H), 1.5-1.7 (m, 4H); ^{13}C NMR (75.5 MHz, C_6D_6) δ 143.0 (s), 142.7 (s), 129.6 (d), 126.6 (d), 126.1 (d), 125.4 (d), 65.5 (d), 58.7 (t), 58.0 (t), 35.3 (t), 30.6 (t), 28.8 (t), 23.6 (t); IR (thin film) 3060, 3020, 2928, 2786, 1491, 1451, 1121, 1105, 759, 740 cm^{-1}. Low resolution mass spectrum (gc-ms) *m/e* (rel abundance) 187 (M^+, 92), 186 (100), 158 (77), 115 (49).

Tricyclic amine 8 from 6c. The TBDMS ether **6c** (38 mg, 0.12 mmol) in THF (1 mL) was treated with TBAF (300 µL, 0.3 mmol, 1M in THF) and allowed to stir at rt for 30 min. The solvent was removed *in vacuo* and the residue was partitioned between ethyl acetate and aqueous $NaHCO_3$ (20%). The organic layer was separated, dried (Na_2SO_4), and concentrated to a crude

oil. Silica gel chromatography (hexane/ethyl acetate/methanol/TEA 2:2:1:1) provided 16 mg (67%) of the amino alcohol as a colorless solid which was partially characterized: ^{1}H NMR (300 MHz, C_6D_6) δ 6.9-7.0 (m, 4H), 3.7-3.8 (m, 1H), 3.55-3.65 (m, 1H), 3.51 (dd, J = 3.2, 9.6 Hz, 1H), 2.91 (dt, J = 4.1, 14.2 Hz, 1H), 2.4-2.7 (m, 5H), 1.5-1.9 (m, 4H), 1.2-1.4 (m, 1H), 0.95-1.15 (m, 1H); ^{13}C NMR (75.5 MHz, C_6D_6) δ 145.7 (s), 142.3 (s), 129.6 (d), 126.8 (d), 126.2 (d), 125.4 (d), 62.9 (t), 61.0 (d), 50.4 (t), 35.4 (t), 32.6 (t), 32.1 (t), 30.0 (t). The alcohol (16 mg, 0.08 mmol) was taken up in THF (1 mL), treated with PBr_3 (14.5 μL, 0.08 mmol) and stirred at rt overnight. The solvent was removed *in vacuo* and the residue was partitioned between ethyl acetate and aqueous $NaHCO_3$. The organic layer was separated, dried (Na_2SO_4), and concentrated to a crude oil which was purified by silica gel chromatography (hexane/ethyl acetate/TEA 17:2:1) to give 9 mg (62%) of the amine as a colorless oil: $[\alpha]_D$ = + 15.2 (c = 0.5, benzene); all spectra were identical to that reported above.

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