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ENANTIOSELECTIVE ALKYLATION OF α-AMINO CARBANIONS

THE SYNTHESIS OF (S)-1-ALKYL-1, 2, 3, 4 TETRAHYDROISOQUINOLINES

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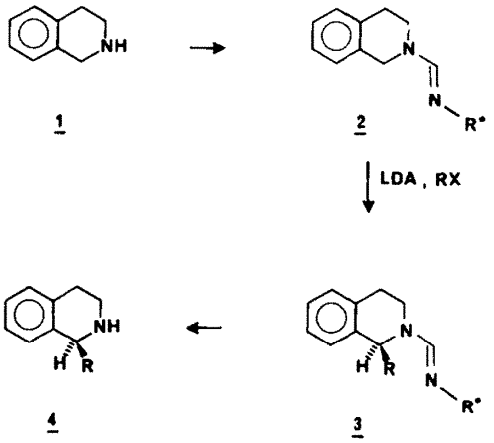
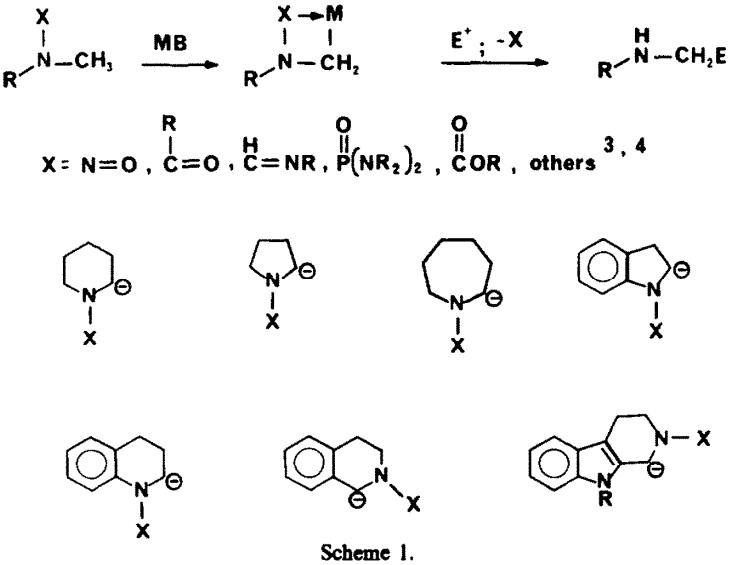
Abstract—A series of chiral amino alcohols transformed into the formamidine derivative of 1, 2, 3, 4-tetrahydroisoquinolines were evaluated as chiral dipole-stabilized anions. Alkylation with alkyl halides provided the 1-alkyl-1, 2, 3, 4-tetrahydroisoquinolines in both excellent yield and enantiomeric purity.

The procession of efficient asymmetric syntheses in recent years has demonstrated that this methodology can now be counted among the accepted routes to chiral non-racemic compounds.[1] Most prominent among these synthetic achievements has been the remarkable success in forming enantioselective C–C bonds which must be regarded as the cornerstone for molecular construction.[2] To date there has been no enantioselective C–C bond method derived from the currently popular and synthetically useful dipole stabilized carbanions (Scheme 1).[3] This species has received much attention due to its ability to generate carbanions α-to N and thus make accessible a wide variety of elaborated N-heterocycles and related alkaloidal systems.[4] In a preliminary report[5] we described the transformation of tetrahydroisoquinoline **1** to its formamidine **2** containing a chiral *R* grouping and subsequent metalation–alkylation to **3**. Removal of the chiral auxiliary provided the 1-alkyl tetrahydroisoquinoline **4** in 90–99% enantiomeric excess. We now relate additional studies which involved a number of chiral auxiliaries and improved experimental details for carrying out this unprecedented enantioselective synthesis.

Preparation of chiral auxiliaries and chiral formamidines

Since a major requirement for a successful asymmetric synthesis involving stoichiometric ratios of chiral inducing groups must be its expense and

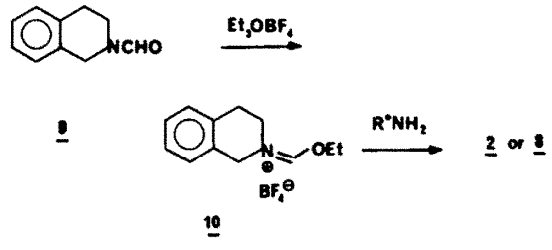


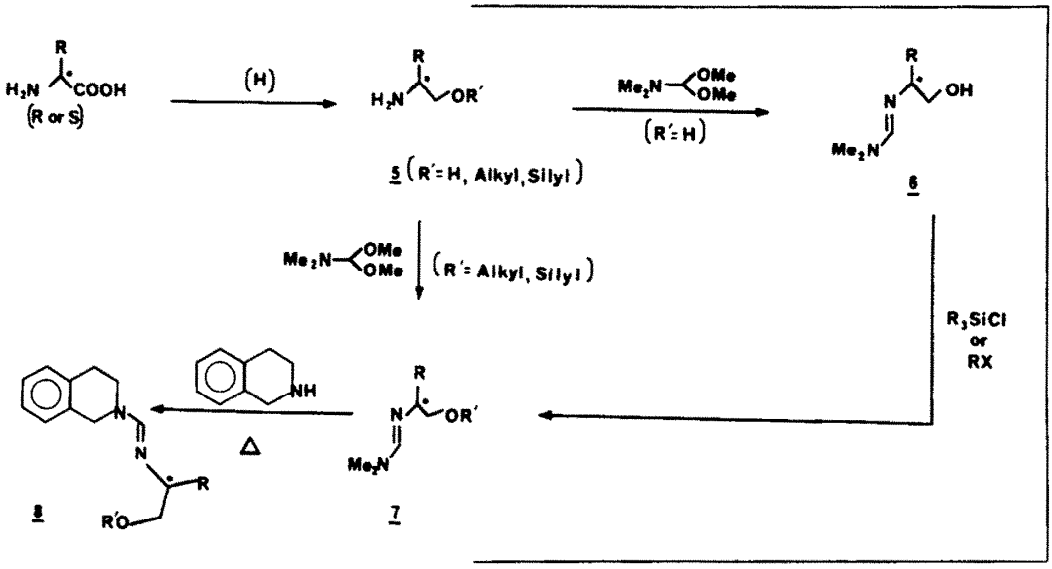


Scheme 1.

availability, we evaluated readily accessible amino acids and related commercial amines which could be easily transformed into formamidines **2** (R* = chiral source). In view of the fact that many amino acids could be smoothly reduced to amino alcohols (**5**) without racemization,[6] and the primary alcohol function could be readily etherified, we felt this is a viable route to the chiral amine moiety in formamidines **2**. Furthermore, formamidines have been prepared in various ways[7] and the route we have chosen in going from **1**→**2** was based on two methods examined in detail. The method of choice is to treat the chiral amino alcohol **5** (R′ = H) with dimethylformamide dimethylacetal furnishing the formamidine alcohol **6** which is then alkylated (e.g. Et_3SiCl) to the formamidine **7**. With or without isolation, the latter was heated with tetrahydroisoquinoline in toluene to generate, in excellent yield, the chiral formamidine of the isoquinoline, **8**.[8] Table 1 reveals the large number of derivatives of **8** which were prepared in this manner. Alternatively, the amino alcohol **5** (R = H) can be protected as its ether (or silyl ether using hexamethyldisilazane) to **5** (R′ = alkyl, silyl) and then heated with DMF acetal forming **7**. This approach, however, has a slight disadvantage in that the labile silyl ethers, may cleave to a small extent during the formamidine step. In two cases the dimethyl formamidines **7** derived from valinol were isolated and characterized (**7a**, **7b**). All the amino alcohols in Tables 1 and 2 are commercially available and it was necessary only to alkylate the hydroxyl function before or after their transformation to the N, N-dimethyl formamidine.

The other approach to chiral isoquinoline formamidine taken was to utilize the N-formyl derivative of the isoquinoline **9** and after treatment with the Meerwein reagent gave the imidate salt **10**. Addition of the amine followed by alkaline work-up led to the formamidines **2**, or **8**. A series of chiral amines was attached to the isoquinoline as their formamidines in this manner and is shown in Table 2. The major limitation of the imidate route is the sensitivity of silyl groups on the amine which tend to cleave in the presence of fluoroboric acid. The low (70%) yield for the BISPAD derivative in the Table is exemplary.





Metalation–alkylation to chiral 1-*substituted*-1, 2, 3, 4-*tetrahydroisoquinolines*

With a variety of chiral auxiliaries now available it remained only to assess their relative effects on the asymmetric alkylation of the 1-position. Metalation of **2** to the 1-lithio derivative **11** was readily accomplished in quantitative yield using lithium diisopropylamide (LDA) in THF at −78°. All the formamidines listed on Tables 1 and 2 responded to these metalation conditions except the formamidine derived from phenylalininol (Table 2, entry 3). In this

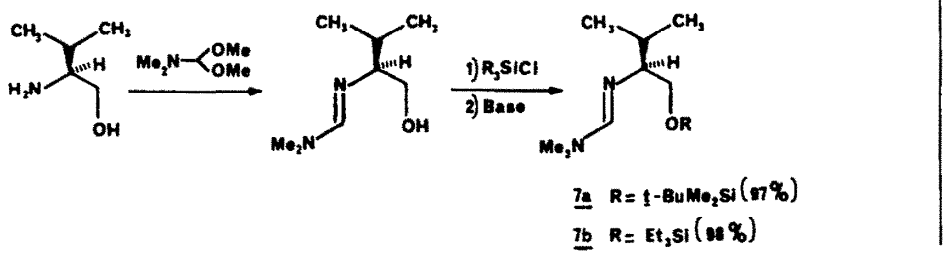
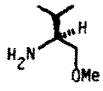
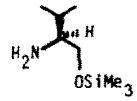
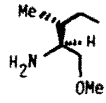
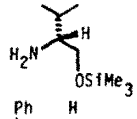
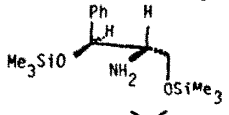
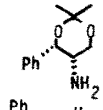
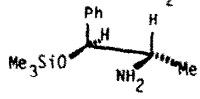
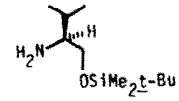
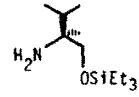
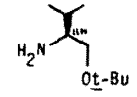
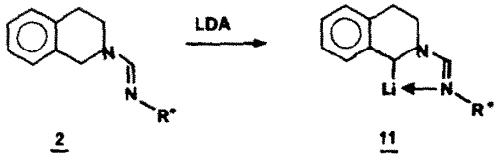


Table 1. Reaction of tetrahydroisoquinoline 1 with dimethylformamidines 7

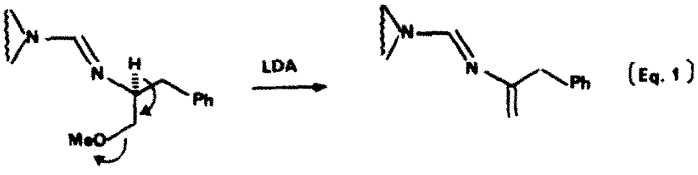
Entry	Chiral Amine in 7	% 8	$[\alpha]_D$ (C, Solvent)
1		99	-62.7° (9.7, $CHCl_3$)
2		96	-21.7° (15.6, $CHCl_3$)
3		99	-66.7° (11.2, $CHCl_3$)
4		96	+25.1° (2.5, $CHCl_3$)
5	 (BISPAD)	95	+49.4° (9.53, THF)
6		95	+160.1° (2.12, THF)
7		87	-75.1° (1.54, THF)
8		93	+8.80° (1.66, THF)
9		96	-2.91° (4.40, THF)
10		95	-3.96° (1.06, THF)



2 11

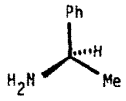
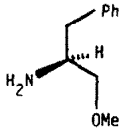
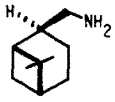
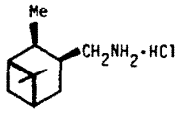
instance metalation led to the elimination of the methoxyl group, presumably via proton abstraction at the chiral carbon (eqn 1). The identification of phenyl acetone, after aqueous quench, supported this contention.[9]

Alkylation of **11** was performed after cooling the lithio compound to −100 and addition of alkyl halides which gave the 1-substituted tetrahydroisoquinolines **3** in excellent chemical yields. The crude product was usually sufficiently clean to proceed onto the formamidine cleavage to **4**. It was observed that the enantioselective alkylations were best at −100° since alkylation at higher temperatures resulted in poor selectivity. The formamidines **3** were readily cleaved to the free amine **4** using hydrazine in ethanol–acetic acid (pH = 8) giving high yields of *both* the isoquinoline and the recovered chiral amine

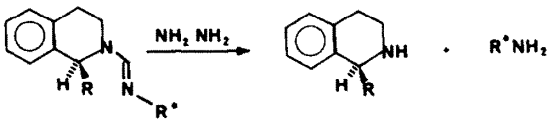


(Eq. 1)

Table 2. Chiral formamidines **2** *via* imidates **10**

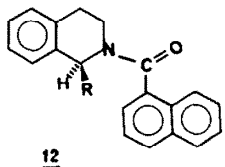
Entry	R^*NH_2	% 2 or 8	$[\alpha]_D$ (C, Solvent)
1		98	-64.9°(3.38,THF)
2	BISPAD (see Table 1)	70	+49.34°(9.64,THF)
3		94	-138.3°(5.24,THF)
4		97.5	-6.58°(3.48,THF)
5		97.4	-15.90°(3.88,THF)

auxiliary. These are conveniently separated on radial chromatography (silica gel) with ethyl acetate.



3 **4** **5**

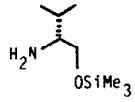
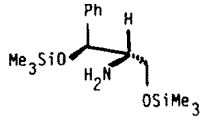
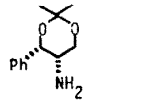
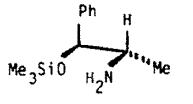
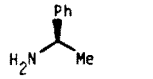
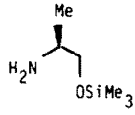
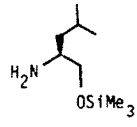
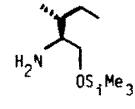
The enantiomeric excess of the alkyl tetrahydroisoquinolines were determined using the covalent Pirkle chiral column[10] by formation of the 1-naphthoyl amides **12** and elution with isopropanol–hexane. The racemic 1-alkylisoquinolines (±)-**4** were prepared from **3** ($R^* = t-Bu$), converted to **12**, and injection onto the chiral HPLC column to produce base line separation of the two enantiomers. This was followed by the injection of **12**, prepared using chiral formamidines and integrating the peak ratios. A typical run for racemic and asymmetrically prepared product is given in Fig. 1. The ratio for the latter is 96.7:3.3 (93.3% ee).



12

With the analytical tool to evaluate enantioselective efficiency available, a study was initiated to test the efficacy of the various chiral groups toward the alkylation with methyl iodide. The results are given in Table 3. The absolute configurations for the product **4** (R = Me) is based on the asymmetric synthesis of the benzo[a]quinolizine (*vide supra*). Furthermore, the *S*-enantiomer was observed to elute through the chiral Pirkle column *after* the *R*-enantiomer thus making assignments very simple. The enantioselective methylations in Table 3 show a

Table 3. Reaction of 2 with LDA (−78°) and MeI (−100°) to give 1-methyl-1, 2, 3, 4-tetrahydroisoquinoline 4 (R = Me)

Entry	Chiral Amine in 2 or 8	% Chem. Yield	%ee (Conf'n)[b]
	 (S-Valinol)		
1	R = $SiMe_3$	52	88 (S)
2	R = $SiMe_2t$-Bu	74	75 (S)
3	R = $SiEt_3$	70	74 (S)
4	R = t-Bu	90	86 (S)
5	R = Me	46[c]	84 (S)
6	 (R-Valinol)	73	93 (R)
7	 (S,S-BISPAD)	79	>99 (S)
8	 (S,S-PAD)	77	12 (R)
9	 (nor-↓-ephedrine)	74	39 (R)
10	 (S-PEA)	85	10 (R)
11	 (S-alaninol)	60	50 (S)
12	 (S-leucinol)	71	93 (S)
13	 (isoleucinol)	71	90 (S)

a) The chemical yields are based on 2. b) Configurations assigned on R-enantiomer of the naphthoylamide 12 eluting before the S-enantiomer. c) Low yield due to methoxy elimination during the metalation step.

Table 4. 1-Alkyl-1, 2, 3, 4-tetrahydroisoquinolines 4 from S, S-BISPAD

Alkyl Halide[a]	% Chem. Yield 4	%ee[b] (Conf'n)[c]
MeI	80	>99 (S)
i-BuI	85	91 (S)
n-BuBr	80	91 (S)
$PhCH_2Br$	70	93 (S)
$PhCH_2CH_2Br$	65	>99 (S)

a) Alkyl halides added at -100°. b) From integration of the N-napnthoyl amides on chiral HPLC column, compared with racemates. c) Based on order of elution R-enantiomer > S-enantiomer.

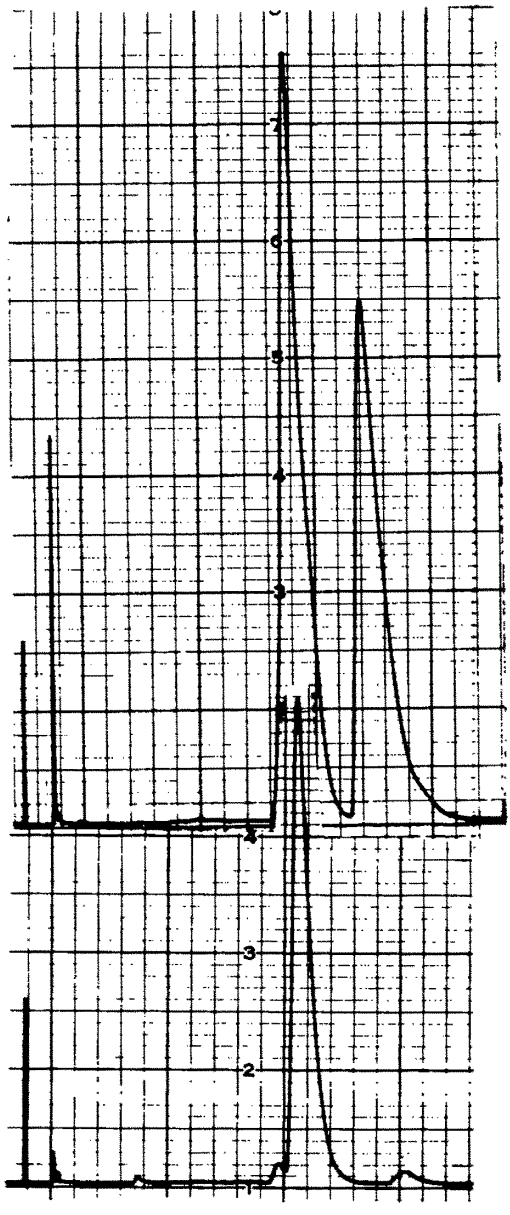
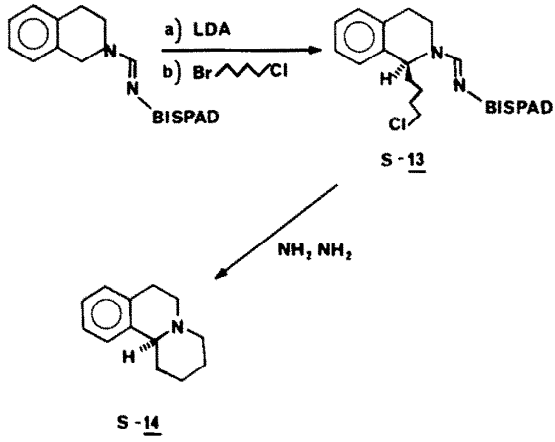


Fig. 1.

wide trend of stereoselectivity with BISPAD (entry 7) furnishing virtually complete selectivity and *S*-phenylethyl amine (entry 10) providing the poorest result. The valinol derivatives (entries 1–6) provide quite reasonable stereoselectivity and use of the enantiomeric valinol (entry 6) provides the optical antipode in comparable ee. The major problem using the valinol silyl derivatives (entries 1–3) was the general loss of the silicon substituent and thus the lower chemical yields for the process. Introducing the t-Bu group, however, appears to solve this problem with a 90% chemical yield observed (entry 4). The enantioselective alkylation is also in the satisfactory range (86%) thus making the t-butyl valinol a viable chiral auxiliary for further study. Similar replacements of the silicon on leucinol (entry 12) with t-Bu should prove interesting. By far and away, however, the *S*, *S*-BISPAD, readily available from commercial sources as the diol, proved to be the most efficient chiral auxiliary to date. In view of the complete enantioselective alkylation using BISPAD, we examined this process with other alkyl halides. The results are given on Table 4. Based on the HPLC analyses with the chiral column, the %ee's are rather pleasing. Finally, the asymmetric process was extended to a synthesis of the benzoquinolizine **14** by metalation and alkylation of the BISPAD-formamidine with 1-bromo-4-chlorobutane to give the chlorobutyl derivative **13**. By removing the chiral amidine with hydrazine, this proceeds directly to the ring closure product in 70% overall yield. Comparison with the known material, obtained by degradation of verosecurine[11] proved to be the *S*-enantiomer in 90% ee. The fact that the *S*-enantiomer of **14** was formed strongly lends support to the initial alkylation to **13** by other alkyl halides proceeding to the *S*-enantiomer. This is in accord with the absolute configurations assigned by the order of elution from the chiral HPLC column.



At this juncture in the study, the complete mechanistic picture is not in hand to comprehend the nature of the high enantioselective alkylation and time constraints put on this manuscript for this volume on enantioselective synthesis will force us to delay until a future report the data we are now accumulating on this potentially very valuable process.

EXPERIMENTAL

M. pts are uncorrected. IR were recorded on a Beckman 4200 spectrometer. PMR and CMR were obtained on a JEOL FX100Q spectrometer. Line positions are given in ppm scale, with internal TMS as standard; the multiplicity, peak areas, and coupling constants are given in parentheses. In the presence of trimethylsilyl ethers, integration was done *prior to the addition of TMS* as internal standard. A VG Micromass 16F mass spectrometer provided the mass spectra.

VPC analyses were performed on a Hewlett Packard 5750 instrument. HPLC analyses were performed on a Waters Associates 440 instrument at a 254 nm wavelength. Radial chromatography (Chromatotron Model 7924) was performed using silica gel PF-254. The support for column chromatography was J. T. Baker 60–200 mesh. Elemental analyses were performed by MicAnal Organic Microanalysis, Tucson, Arizona.

Preparation of (1S, 2S)-1-*phenyl*-2-*amino*-1, 3-*bistrimethylsilyloxypropane* (*BISPAD*)

Into a 250 ml round bottomed flask flame dried under argon was placed 4.396 g (26.28 mmole) of 1*S*, 2*S*-1-phenyl-2-amino-1, 3-propane diol (Aldrich) [m.p. 112–112.5°, $[\alpha]_C^{24} + 26.65$ ($c = 6.6$, MeOH)][12]. Via syringe was added 13.9 ml (65.70 mmole, 2.5 equiv) of hexamethyldisilazane. The mixture was slowly warmed up to reflux temp. (140°). After refluxing 8 hr, the oil bath was removed and when the crude mixture reached room temp. 20 ml of sat $NaHCO_3$aq were added and stirred for $\frac{1}{2}$ hr. The organic layer was extracted and the aqueous layer back extracted (2 × 25 ml) with CH_2Cl_2. The organic layer was extracted and the aqueous layer back extracted (2 × 25 ml) with CH_2Cl_2. The combined organic layers were dried over K_2CO_3. The solvent, CH_2Cl_2, and hexamethyldisiloxane (b.p. 101°) were removed by distillation. Distillation at reduced pressure (b.p. 120–123°/0.025 mm) afford 8.020 g (98.1%) of pure product. VPC: 6 ft = $\frac{1}{4}$ in., 10% SE-52 suspended on Chromosorb W column with a temp program 100–300°@ 15°/min showed only one peak, RT 10.0 min.

IR (film) 3280, 2870, 1245, 1095, 1080, 1060, 1045, 830, 740, 695 cm^{-1}. Mass Spectrum (70 eV) *m/e* (rel. int.): 296 (0.7, M-16, $-NH_2$), 208 (6.1), 20 (5.6), 179 (7.9), 146 (6.4), 133.1 (11.4), 132 (100.0), 118 (10.5), 117 (7.0), 116 (51.0). ^{13}C NMR ($CDCl_3$, TMS) 142.5, 127.9, 126.9, 124.7, 75.4, 63.1, 58.7, 0.3, −0.4 ppm. ^1H NMR ($CDCl_3$, TMS) 7.15 (5H, s), 4.64 (1H, d, $J = 6.15$ Hz), 3.38–3.18 (H, ABX pattern, $J_{AX} = 6.20$ Hz, $J_{BX} = 7.57$ Hz, $J_{AB} = 11.72$ Hz), 2.76 (1H, m), 1.51 (2H, broad s), 0.09 (9H, s), 0.00 (9H, s) ppm. $[\alpha]_D^{24} + 47.46$ (c = 9.32, $CHCl_3$), $[\alpha]_D^{24} + 45.44$ (c = 23.78, THF). Calc for $C_{15}H_{29}O_2NSi_2$: C, 57.81; H, 9.40; N, 4.50%). (Found: C, 57.96; H, 9.28; N, 4.33.

Preparation of (1S, 2S) 1-*phenyl*-1-*trimethylsilyloxy*-2-*amino propane* (Table 1, entry 7)

(−)-Norpseudoephedrine hydrochloride (2.119 g, 11.29 mmole) was placed in a 100 ml flask under N_2 with a reflux condenser. To the solid was added 6.0 ml of hexamethyldisilazane (28–33 mmole) followed by 5 ml Et_3N and 10 ml of dichloroethane. The mixture was refluxed for 4 hr; then poured over sat $NaHCO_3$aq. The organic phase was separated and the aqueous extracted with CH_2Cl_2. The combined organic layers were dried over K_2CO_3. The crude product was distilled (bulb to bulb, b.p. 125°/0.10 mm) to afford 2.296 g (91.1%) of the desired product. VPC: 6 ft × $\frac{1}{4}$ in., 10% SE-52 suspended on Chromosorb W column with a temp program 100–300°/@15°/min showed only one peak, RT = 7.6 min.

^1H NMR ($CDCl_3$) 7.26 (s, 5H), 4.28 (d, 1H, $J = 6.10$ Hz), 2.94 (m, 1H), 1.64 (s, 2H, NH_2), 0.93 (d, 3H, $J = 6.59$ Hz), 0.00 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, TMS) 142.7, 127.9, 127.2, 126.6, 80.7, 53.6, 19.5, 0.2 ppm. $[\alpha]_D^{24} = -64.25$ (c = 3.91, THF).

Preparation of t-butyl ether L-valinol

In a 500 ml pressure bottle with a magnetic stirrer was placed 2.364 g (22.91 mmole) of L-Valinol in 25 ml of dioxane and 2.5 ml of H_2SO_4. The mixture solidified at −78°, and 25 ml of liquid isobutene was condensed and the pressure bottle sealed. The mixture was warmed up to rt and stirred for 8 hr. The mixture was cooled back to −78° to open the pressure bottle. The soln was poured immediately into a cold mixture of 200 ml of ether and 125 ml of 20% NaOH, and the aqueous phase was washed with ether. The ether soln was dried over K_2CO_3 and evaporated under vacuum to about 5 ml. This was diluted with 25 ml of ether. Addition of dry HCl and evaporation of the ether gave the crystalline hydrochloride in 29% yield, m.p. 142.5–144°.

^1H NMR ($CDCl_3$, TMS) 7.69 (s, 2H); 3.55 (m, 2H); 2.58 (m, 1H); 1.43 (m, 1H); 1.23 (s, 9H); 1.19, 1.05 (d, 3H) ppm. ^{13}C NMR ($CDCl_3$, TMS) 73.6, 59.7, 57.7, 28.4, 27.,5, 19.2 ppm. $[\alpha]_D^{24} = +8.83°$ ($c = 0.77$, $CHCl_3$). (Found: C, 55.25; H, 10.81; N, 7.10. Calc for C_9H_2NOCl: C, 55.20; H, 11.35; N, 16%).

Preparation of N′-*chiral auxiliary*-N, N-dimethylformamidines

General procedure 7 To the amino alcohol (1.0 equiv) was added the N, N-dimethylformamide dimethyl acetal (1.1 equiv) and heated to 40° for 1–2 hr. The reaction was followed by VPC until complete disappearance of the amino alcohol. The crude mixture was concentrated and used without further purification for the protection of the alcohol. The crude product was dissolved in CH_2Cl_2 (~ 1 ml/mmole) and 1.0 equiv of the corresponding chlorosilane was added to an equal volume of CH_2Cl_2 at a rate to maintain a gentle reflux. After complete addition, the reaction was stirred for at least 1 hr. To the mixture at 0° was added 20% NaOH (10 equiv) and extracted with CH_2Cl_2. The combined organic layers were dried (K_2CO_3) and concentrated to give the product generally as a yellow oil. The crude product was purified by column chromatography on silica gel (5% Et_3N/hexane). The same procedure was used for amino ethers. The crude product can be used without further purification for the next step.

N′-(S)-1-*t*-*Butyldimethylsilyloxy*-2-*amino*-3-*methyl*-1-*butane*-N, N-*dimethylformamidine*, 7

L-valinol, 7.747 g (75.09 mmole) was treated with 10.6 ml (9.53 g, 80.0 mmole) of N, N-dimethylformamide-dimethyl acetal (DMF–acetal) according to the general procedure. The mixture was concentrated to remove the MeOH and the excess of DMF–acetal. The crude product was dissolved in 75 ml of CH_2Cl_2 and at 0° 11.405 g (75.67 mmole) of t-$BuMe_2SiCl$ was added in portions. After column chromatography, 20.850 g (97.0%) of pure product was isolated. VPC: 10% SE-52 suspended on A Chromosorb W column with a temperature program 100–300° @ 15°/min shows only one peak, RT 8.82 min.

IR (film) 2960, 2930, 2860, 1660, 1370, 1260, 1100 cm^{-1}. ^1H NMR ($CDCl_3$) 7.16 (s, 1H), 3.65–3.28 (m, 3H), 2.78 (s, 6H), 1.69 (m, 1H), 0.84 (s, 15H), 0.00 (s, 6H) ppm. ^{13}C NMR ($CDCl_3$, TMS) 154.2, 73.2, 66.1, 37.1, 30.1, 26.0, 20.3, 18.8, 18.4, −5.1 ppm; $[\alpha]_D^{24} = -3.37$ ($c = 5.88$, THF).

N′-(S)-1-*Triethylsilyloxy*-2-*amino*-3-*methyl*-1-*butane*-N, N-*dimethylformamidine*

L-valinol, 4.806 g (46.58 mmole) was treated with 6.6 ml (5.96 g, 500 mmole) of the DMF-acetal according to the general procedure. The mixture was concentrated to remove the MeOH and excess of DMF-acetal. The crude product was dissolved in 50 ml of CH_2Cl_2 and at 0° 7.7 ml of triethylchlorosilane (6.90 g, 45.8 mmole) was added. After column chromatography purification, 12.267 g (98.3%) of pure product was isolated. VPC: 6 ft × $\frac{1}{4}$ in., 10% SE-52 suspended on Chromosorb W column with a temperature program 100–300° @ 15°/min shows only one peak, RT 8.7 min.

IR (film) 2950, 2900, 2870, 1655, 1360, 1100 cm^{-1}. $[\alpha]_D^{24}$ 8.90 ($c = 1.46$, THF).

N′-(S, S)*BISPAD*-N, N-*dimethylformamidine*

To 67.50 g (216.6 mmole) of BISPAD was added 30.6 ml of the DMF acetal (27.41 g, 230.0 mmole) following the general procedure. Bulb to bulb distillation, b.p. 125–130°/0.10 mm afforded 76.411 g (96.2%) of pure product. VPC: 6 ft × $\frac{1}{4}$ in., 10% SE-52 suspended on Chromosorb W column with a temperature program 100–300° @ 15°/min shows only one peak, RT 13.3 min.

IR (film) 3010, 2950, 1650, 1370, 1080 cm^{-1}. $[\alpha]_D^{24} + 68.17$ ($c = 12.85$, THF); $[\alpha]_D^{24} + 54.65$ ($c = 1.57$, THF). $[\alpha]_D$ is concentration dependent.

N′-(4S, 5S)-(+)-5-*Amino*-2,-*dimethyl*-4-*phenyl*-1, 3-*dioxane*-N, N-*dimethylformamidine*

To 24.332 g (117.38 mmole) of (4*S*, 5*S*)-(+)-5-amino-2, 2-dimethyl-4-phenyl-1,3-dioxane (Aldrich) was added 17.3 ml of DMF–acetal (15.50 g, 130.0 mmole) following the general procedure. Bulb to bulb distillation, b.p.

128–30°/0.10 mm gave 30.224 g (98.2%) of pure product. VPC: 6 ft × ¼ in. 10% SE-52 suspended on a Chromosorb W column with a temperature program 100–300°C @ 15°/min, holding the limit shows only one peak, RT = 17.3 min., m.p. 56–7°.

IR (film) 3010, 2990, 2860, 1650, 1375 cm^{-1}. ^1H NMR ($CDCl_3$, TMS) 7.25 (s, 5H), 7.00 (s, 1H); 5.15 (d, 1H, J = 2.68 Hz), 4.20 (A of AB, 1H, J_{AB} = 11.72 Hz, J_{AC} = 3.42 Hz), 3.86 (B of AB, 1H, J_{BA} = 11.72 Hz, J_{BC} = 3.42 Hz); 3.25 (m, 1H), 2.63 (s, 6H), 0.57 (s, 6H) ppm. ^{13}C NMR ($CDCl_3$, TMS) 154.9, 139.8, 127.4, 127.0, 126.6, 99.1, 74.7, 66.3, 61.1, 36.8, 29.0, 19.8 ppm. $[\alpha]_D$ + 177.33° (c = 6.07, THF).

Preparation of N-*formyl*-1, 2, 3, 4-*tetrahydroisoquinoline* (9)[13]

Ethyl formate (24.2 ml, 300.0 mmol) was added slowly with cooling to 1, 2, 3, 4-tetrahydroisoquinoline (32.6 g, 244.76 mmol) and after the exothermal reaction has ceased, the soln was refluxed for 2 hr. The excess of ethyl formate and the EtOH generated was removed in the aspirator and the crude product distilled at reduced pressure (bp 110°/0.0 mm) to afford 38.22 g (97.1%) of pure product. VPC: 6 ft × ¼ in., 30% SE-30 suspended on a Chromosorb W column with a temperature program 100–250° @ 15°/min shows only one peak, RT 3.7 min.

IR (film) 3060, 3020, 2930, 2850, 1670, 1440, 1400, 1200, 750 cm^{-1}. ^1H NMR ($CDCl_3$, TMS): 8.22 (s) and 8.17 (s), (1H), 7.17 (s, 4H), 4.63, 4.48 (s each, 2H total); 3.73, 3.60 (t each, J = 6Hz, 2H total), 2.85 (t, J = 6 Hz, 2H), ppm.

Preparation of N′-*chiral auxiliary*-1, 2, 3, 4-*tetrahydroisoquinoline formamidines*

General procedure using Et_3OBF_4. To a soln of Et_3OBF_4 (> 1.1 equiv) in dichloroethane (~ 5 ml/g of amide) was added to the N-formyl-1, 2, 3, 4-tetrahydroisoquinoline (1.0 equiv). After stirring at room temp overnight, the chiral amine (1.05 equiv) was added dropwise. If the chiral amine is acid sensitive or a hydrochloride salt, 5.0 equiv of Et_3N was added prior to the addition of the chiral amine. The addition led to an exothermic reaction. Subsequently, the mixture was stirred at room temp for at least 5 hr. The mixture was poured into 20% NaOH (10 equiv) and extracted with CH_2Cl_2. The combined organic layers were washed (water), dried (K_2CO_3) and concentrated to give the crude product generally as a yellow oil. The crude product was purified by column chromatography on silica gel (10% Et_3N/hexane) followed by (bulb-to-bulb) distillation.

N′d-(+)(α-*Methylbenzylamino*-1, 2, 3, 4-*tetrahydroisoquinoline formamidine* (2 or 8)

N-formyl-1, 2, 3, 4-tetrahydroisoquinoline (2.42 g, 15.0 mmol) was treated with Et_3OBF_4 (4.12 g, 21.69 mmol) and d-(+)-α-methylbenzylamine [1.94 ml, 15.0 mmol, $[\alpha]_D^{23}$ + 38° (neat)] according to the general procedure. The crude product was distilled to give 3.89 g (98.6%) as a colorless oil; b.p. 179–183°/0.05 mm.

IR (film) 3040, 3010, 2950, 2910, 2840, 2820, 1635, 1445, 1375, 1195, 740, 700 cm^{-1}. ^1H NMR ($CDCl_3$/TMS): 7.53 (s, 1H), 7.46–6.97 (m, 9H), 4.53 (s, 2H), 4.30 (q, 1H, J = 7 Hz), 3.50 (t, 2H, J = 7 Hz), 2.83 (t, 2H, J = 7 Hz), 1.48 (d, 3H, J = 7 Hz) ppm. ^{13}C NMR ($CDCl_3$/TMS) 152.8, 147.2, 134.3, 133.3, 128.6, 127.9, 126.1, 125.9, 64.3, 46.7, 44.3, 29.2, 26.1 ppm. $[\alpha]_D^{20} = -64.94°$ (c = 3.38, THF). (Found: C, 79.49; H, 7.70; N, 10.35. Calc for $C_{18}H_{20}N_2$: C, 81.76; H, 7.64; N, 10.60%). Formamidines, in general, gave poor elemental analyses due to their moisture sensitivity.

Isoquinoline 2 (R = BISPAD)

N-formyl-1, 2, 3, 4-tetrahydroisoquinoline (3.71 g, 23.00 mmol) was treated with Et_3OBF_4 (5.98 g, 31.49 mmole), Et_3N (16.0 ml, 115 mmol) and 1*S*, 2*S*)-1-phenyl-2-amino-1, 3-bistrimethylsilyloxypropane (8.00 g, 25.67 mmol) according to the general procedure. The crude product was distilled to give a colorless oil; 7.396 g (70.7%): b.p. 110°/> 0.001 mm.

IR (film) 3060, 3020, 2950, 1640, 1490, 1380, 1250, 1070, 875, 840, 745, 70 cm^{-1}. ^1H NMR ($CDCl_3$, TMS) 7.32–7.10 (m, 10H), 4.70 (d, 1H, J = 6.10 Hz), 4.56 (s, 2H), 3.56–2.90 (m, 7H), 0.05 (s, 9H), 0.00 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, TMS) 154.8, 143.0, 134.5, 133.5, 128.6, 127.6, 126.9, 126.7, 126.3, 126.0, 76.1, 74.1, 64.2, 46.6, 44.3, 29.3, +0.4, −0.1 ppm. $[\alpha]_D^{24}$ + 49.34° (c = 9.64, THF).

Preparation of N′-chiral auxiliary-1, 2, 3, 4-*tetrahydroisoquinoline* 8

General procedure using exchange reaction. To 1.0 equiv of the N′-chiral auxiliary-N, N-dimethylformamidine in toluene (1 ml/mmole) was added 1, 2, 3, 4-tetrahydroisoquinoline (1.5 equiv) and refluxed until complete conversion of the N, N-dimethylformamidine. For an acid catalyst, a few crystals of $(NH_4)_2SO_4$ are strongly recommended. The reaction is followed by VPC or the absence of dimethyl amine evolution from the top of the condenser (wet litmus paper).

N′-(2*R*)-1-*Trimethylsilyloxy*-2-*amino*-3-*methylbutane*-1, 2, 3, 4-*tetrahydroisoquinoline* (Table 1, entry 4)

N′-(2R)-1-trimethylsilyloxy-2-amino-3-methylbutane-N, N-dimethylformamidine (9.02 mmole), generated *in situ*, and 1, 2, 3, 4-tetrahydroisoquinoline (10.0 mmol) in 10 ml of toluene were refluxed for 4 hr. The crude product was purified by column chromatography (20% Et_3N/hexanes) followed by distillation, b.p. 130°/0.5 mm, to afford 2.757 g (8.65 mmole, 95.9%).

IR (film) 3005, 2950, 2860, 1650, 1450, 1380, 1245, 1100 cm^{-1}. ^1H NMR ($CDCl_3$) 7.31 (s, 1H), 7.07 (s, 4H), 4.45 (s, 2H), 3.78–3.08 (m, 4H), 2.85–2.311 (m, 3H), 1.67 (q, 1H, J = 6.49 Hz), 0.80 (d, 6H, J = 6.49 Hz), 0.00 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, TMS): 153.5, 134.6, 133.6, 128.7, 126.3, 126.0, 76.4, 65.7, 46.9, 44.4, 30.1, 29.3, 20.4, 18.8, −0.1ppm. $[\alpha]_D^{24}$ + 11.89° (c = 4.13, CH_2Cl_2): $[\alpha]_D^{24}$ + 25.12° (c = 2.52, $CHCl_3$).

N′-(4*S*, 5*S*)-(+)-5-*Amino*-2, 2-*dimethyl*-4-*phenyl*-1, 3-*dioxane*-1, 2, 3, 4-*tetrahydroisoquinoline formamidine* (Table 1, entry 6)

N′-(4*S*, 5*S*)-(+)-5-amino-2, 2-dimethyl-4-phenyl-1, 3-dioxane-N, N-dimethyl formamidine (14.72 mmole, 3.861 g) and 1, 2, 3, 4-tetrahydroisoquinoline (15.00 mmole, 1.997 g) in 8.0 ml of toluene were refluxed for 10 hr. The crude product was purified by column chromatography 5% Et_3N/hexane to afford 4.910 g (95.2%) of product.

IR (film) 3030, 3010, 2995, 2940, 2860, 1650, 1585, 1500, 1450, 1380, 1200 cm^{-1}. ^1H NMR ($CDCl_3$, TMS) 7.27–7.07 (m, 10H), 5.17 (d, 1H, J = 2.93 Hz), 4.56–4.15 (m, 3H), 3.89 (B of AB, 1H, J_{BA} = 11.76 Hz, J_{BC} = 2.44 Hz), 3.26 (m, 3H), 2.61 (m, 2H), 1.58 (s, 6H) ppm. ^{13}C NMR ($CDCl_3$, TMS): 154.2, 139.6, 134.5, 133.6, 128.6, 127.4, 126.8, 126.6, 126.2, 125.9, 99.1, 74.7, 66.1, 61.6, 46.6, 44.0, 29.1, 19.7 ppm. $[\alpha]_D$ + 160.05° (c = 2.12, THF).

N′-(1*S*, 2*S*)-1-*Phenyl*-1-*trimethylsilyloxy*-3-*methocymethyl*-2-*amino propane* 1, 2, 3, 4-*tetrahydroisoquinoline* (Table 1, entry 7)

N′-(1*S*, 2*S*)-1-phenyl-1-trimethylsilyloxy-3-methoxymethyl-2-amino propane-N, N-dimethyl formamidine (9.30 mmole) generated *in situ* and 1, 2, 3, 4-tetrahydroisoquinoline (10.00 mmole) in 10 ml of toluene were refluxed for 10 hr. The crude product was purified by column chromatography (20% Et_3N/hexanes) to afford 3.115 g (8.50 mmole, 86.5%) of the desired product.

IR (film) 3040, 3030, 3010, 2960, 2920, 2900, 2870, 2840, 1650, 1610, 1585, 1500, 1450, 1380, 1250, 1080, 1060 cm^{-1}. ^1H NMR ($CDCl_3$): 7.59 (s, 1H), 7.40–7.00 (m, 9H), 4.63 (s, 2H), 4.44 (d, 1H, J = 7.57 Hz), 3.66–2.80 (m, 5H), 0.98 (d, 3H, J = 6.59 Hz), 0.00 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, TMS) 154.0, 143.2, 134.5, 128.6, 127.7, 127.0,

126.9, 126.3, 126.0, 125.3, 80.0, 67.6, 46.8, 44.5, 29.4, 19.7, 0.3 ppm. $[\alpha]_D = -75.06°$ ($c = 1.54$, THF).

N′-(2S)-1-*t-Butyldimethylsilyloxy-2-amino-3-methylbutane-1, 2, 3, 4-tetrahydroisoquinoline formamidine* (Table 1, entry 8)

N′-(2*S*)-1-t-Butyldimethylsilyloxy-2-amino-3-methylbutane-N, N-dimethyl formamidine (6.812 g, 25.09 mmole) and 1, 2, 3, 4-tetrahydroisoquinoline (3.60 g, 27.00 mmole) in 15 ml of toluene were refluxed for 96 hr. The crude product was purified by column chromatography (5% Et_3N/hexanes) to afford 8.696 g (92.5%).

IR (film) 3030, 3010, 2950, 2925, 2850, 1640, 1460, 1380, 1250, 1100 cm^{-1}. ^1H NMR ($CDCl_3$, TMS) 7.40 (s, 1H), 7.14 (s, 4H), 4.51 (s, 2H), 3.90–3.27 m (4H), 3.09–2.45 (m, 3H), 1.75 (q, 1H, J = 6.59 Hz), 1.02–0.65 (m, 15H), 0.03–0.00 (m, 6H) ppm. $[\alpha]_D + 8.80°$ ($c = 1.66$, THF).

N′-(2S)-*Triethylsilyloxy-2-amino-3-methylbutane-1, 2, 3, 4-tetrahydroiso-quinoline formamidine* (Table 1, entry 9)

N′-(2*S*)-triethylsilyloxy-2-amino-3-methylbutane-N, N-dimethyl formamidine (8.837 g, 32.43 mmole) and 1, 2, 3, 4-tetrahydroisoquinoline (35.00 mmole) in 30 ml of toluene were refluxed for 10 hr. The crude product was purified by column chromatography (5% Et_3N/hexanes) to afford 11.214 g (95.9%) of product.

IR (THF) 3000-2820, 1650, 1450, 1050 cm^{-1} ^1HNMR ($CDCl_3$, TMS): 7.39 (s, 1H), 7.13 (s, 4H), 4.51 (s, 2H), 3.90-3.35 (m, 4H), 2.90–2.41 (m, 3H), 1.49 (m, 1H, J = 7.08 Hz), 0.95–0.31 (m, 21H) ppm. ^{13}CNMR ($CDCl_3$, TMS): 153.9, 134.6, 133.7, 128.7, 126.3, 126.0, 73.7, 65.8, 44.3, 30.2, 20.4, 6.8, 4.6 ppm. $[\alpha]_D^{24}$-2.91° (c = 4.40, THF).

N′-(2S)-t-Butoxy-2-amino-3-methylbutane-1, 2, 3, 4-tetrahydroisoquinoline formamidine (*Table 1, entry 10*)

N′-(2*S*)-t-Butoxy-2-amino-3-methylbutane-N,N-dimethyl formamidine (22.91 mmole) generated *in situ* and 1, 2, 3, 4-tetrahydroisoquinoline (25.0 mmole) in 40 ml of toluene were refluxed for 10 h. The crude product was purified by column chromatography 5% Et_3N/hexanes to afford 5.906 g (95.0%) of product.

IR (film) 3030, 3010, 2970, 2920, 2860, 1650, 1450, 1370, 1360, 1195, 1075 cm^{-1}. ^1H NMR ($CDCl_3$, TMS): 7.41 (s, 1H), 7.13 (s, 4H), 4.50 (s, 2H), 3.77–2.57 (m, 7H), 1.80 (m, 1H), 1.13 (S, 9H), 0.87 (d, 6H, J = 6.59 Hz) ppm. ^{13}C NMR ($CDCl_3$, TMS): 153.7, 134.6, 133.7, 128.7, 126.3, 125.0, 72.5, 71.6, 64.9, 44.4, 30.3, 29.3, 27.8, 20.4, 18.4 ppm. $[\alpha]_D^{24} = -3.96°$ ($c = 1.06$, THF).

Alkylation of chiral formamidines (*General Procedure*)

A dry, round-bottom flask equipped with magnetic stirring, cold bath, and an argon inlet was charged with THF (2 ml/mmol), diisopropylamine (1.25 equiv) and at −78° n-BuLi in hexane (1.25 equiv). The resulting soln was warmed to room temp for 5 min, cooled to −78° again and added via cannula to 0.05 M THF soln of the chiral formamidine (1.0 equiv) previously cooled at −78°. The soln became dark red while stirring at −78° (3 hr). The electrophile (1.25 equiv) was introduced dropwise at the indicated temp. For −78° an acetone/dry ice bath is used and for −100°, MeOH/liquid N_2. The electrophile is allowed to react at the indicated temp as long as it took for the dark red color of the anion to disappear (for alkyl bromides usually 2–3 hr, alkyl iodides 1 hr). The reaction was poured into sat $NaHCO_3$aq and extracted (CH_2Cl_2). The combined organic layer was dried (K_2CO_3), then concentrated to the crude product which was characterized by ^1H NMR and subjected to hydrazinolysis conditions without further purification.

Hydrazinolysis of chiral formamidines (*General Procedure*)

To the chiral formamidine was added 95% hydrazine (3.0 equiv) followed by a soln of glacial AcOH (3.0 equiv) in 60% aqueous EtOH (2 ml/mmol). The pH was checked and when necessary adjusted to 8. After heating overnight, the reaction was diluted (water) and extracted (CH_2Cl_2). The combined organic layers were washed (water), dried (K_2CO_3), then concentrated to the crude product. The crude product was purified by radial chromatography (silica gel PF-254) using EtOAc as eluent. The 1-alkyl-1, 2, 3, 4-tetrahydroisoquinoline was converted to the hydrochloride salt to avoid air oxidation. The chiral auxiliary was recovered chemically and optically pure from the radial chromatograph.

Optical purity determination

Separation of enantiomers of α-naphthoyl derivatives of 1-alkyl-1, 2, 3, 4-tetrahydroisoquinolines on a chiral stationary phase.[10] To the 1-alkyl-1, 2, 3, 4-tetrahydroisoquinoline was added α-naphthoyl chloride (1.5 equiv) in CH_2Cl_2 (2 ml/mmol). The mixture was stirred for 0.5 hr at room temp and poured in 20% NaOH (~ 10 equiv). The organic material was extracted and the aqueous back extracted with CH_2Cl_2 and dried over K_2CO_3. The crude product was purified by radial chromatography (silica gel PF-254) using 10% ETOAc/40% Hexanes/50% CH_2Cl_2 to remove the excess of α-naphthoic acid only. Chromatography is performed using a Waters Associates Model 440 instrument at 254 nm wavelength. The column specifications: Pirkle Covalent Phenylglycine, Modified Spherisorb S5NH (Regis Chem. Co., Skokie, Illinois), 25 cm × 4.6 mm − $\frac{1}{4}$ in. OD, end fittings: $\frac{1}{16}$ in. Swagelok ZDV. The solvent used for the analysis was 10% iPrOH/Hexane, the flow was 6 ml/min with a back pressure of 4000 psi.

Physical properties of 1-alkyl-1, 2, 3, 4-tetrahydroiso-quino-lines

1-Methyl-1, 2, 3, 4-tetrahydroisoquinoline. IR (film) 3650–3160 (broad), 3080, 3040, 2980, 2940, 1490, 750 cm^{-1}. ^1H NMR ($CDCl_3$, TMS): 7.00 (s, 4H), 4.00 (q, 1H, J = 6 Hz), 3.27–2.50 (m, 4H), 1.63 (s, 1H, NH), 1.43 (d, 3H, J = 6 Hz) ppm. Hydrochloride salt: m.p. 183–4° (Found: C, 65.27; H, 7.76; N, 7.55. Calc for $C_{10}H_{14}NCl$: C, 65.38; H, 7.70; N, 7.62%).

1-Iso-butyl-1, 2, 3, 4-tetrahydroisoquinoline. IR (film) 3520–3200 (broad), 3080, 3040, 2980, 2940, 1490, 1460, 740, 730 cm^{-1}. ^1H NMR ($CDCl_3$, TMS): 7.03 (s, 4H), 3.97 (broad t, 1H), 3.33–2.57 (m, 4H), 2.03–1.32 (m, 4H), 1.01 (d, J = 6 Hz), 0.97 (d, J = 6 Hz, 6H) ppm. Hydrochloride salt: 144–6° (Found: C, 68.63; H, 9.11; N, 6.14. Calc for $C_{13}H_{20}NCl$: C, 69.15; H, 8.95; N, 6.20%).

1-Benzyl-1, 2, 3, 4-tetrahydroisoquinoline. IR (film) 3680–3140 (broad), 3080, 3040, 2970, 1495, 1450, 750 cm^{-1}. ^1H NMR ($CDCl_3$, TMS): 7.30–7.00 (m, 9H), 4.31–4.00 (m, 1H), 3.42–2.67 (m, 6H), 1.83 (broad s, 1H, NH) ppm. Hydrochloride salt: m.p. 168–9°.[14]

1-n-Butyl-1, 2, 3, 4-tetrahydroisoquinoline. IR (film) 3600–3160 (broad), 3060, 3020, 2950, 2930, 2860, 1500, 1460, 740 cm^{-1}. ^1H NMR ($CDCl_3$, TMS): 7.00 (s, 4H), 4.10–3.70 (broad t, 1H), 3.43–2.55 (m, 4H), 2.13–0.70 (m, 10H) ppm. Hydrochloride salt: m.p. 143–4°. (Found: C, 69.08; H, 9.10; N, 6.23. Calc for $C_{13}H_{20}NCl$: C, 69.15; H, 8.95; N, 6.20%).

1-Phenylethyl-1, 2, 3, 4-tetrahydroisoquinoline. IR (film) 3600–3140 (broad), 3065, 3040, 2960, 1600, 1490, 1450, 740 cm^{-1}. ^1H NMR ($CDCl_3$, TMS): 7.2 (s, 5H), 7.05 (s, 4H), 3.95 (t, 1H, J = 6 Hz), 3.3–2.60 (m, 6H), 2.20–1.90 (m, 2H), 1.7 (s, 1H, NH) ppm. Hydrochloride salt: m.p. 168–9°. (Found: C, 74.62; H, 7.34; N, 5.00. Calc for $C_{17}H_{20}NCl$: C, 74.54; H, 7.38; N, 5.12%).

1, 3, 4, 6, 7, 11b-Hexahydro-2H-benzo[a]quinolizine. $[\alpha]_D^{23} = -126.2$ (*c* 0.5 EtOH), reported[11] for the *S*-enantiomer, $[\alpha]_D^{23}$-140° (*c* 0.43 EtOH). IR (film) 3040, 3000, 2920, 2840, 2790, 2730, 1490, 1440, 1350, 1295, 1130, 1110, 1050, 725 cm^{-1}. ^1H NMR ($CDCl_3$, TMS): 7.21–7.05 (m, 4H), 3.35–1.14 (m, 13H) ppm. ^{13}C NMR ($CDCl_3$, TMS): 138.1, 134.1, 128.6, 125.7, 125.5, 124.4, 63.3, 57.1, 52.6, 31.2, 29.6, 25.4, 25.0 ppm. Hydrochloride salt: m.p. 260–2°[15].

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