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Intramolecular Hydroaminations Mediated by Reductive Mercuration or *n*-Butyllithium To Afford 3-Methyl- and 3,4-Dimethyl-1,2,3,4-tetrahydroisoquinolines

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The synthesis of 3-methyl- and 3,4-dimethyltetrahydroisoquinolines from aromatic aminoalkenes using intramolecular hydroamination reactions is described. This reaction was achieved by way of a reductive aminomercuration using mercuric acetate followed by sodium borohydride, or by using sub-stoichiometric amounts of *n*-butyllithium.

Introduction

The intramolecular addition of an amine or amine equivalent to an unsaturated carbon fragment (alkene, alkyne or allene) has seen much investigation in the last few years.[1] Recently developed methodologies include the use of many elements in the Periodic Table. Examples including transition metals, e.g. rhodium,[2] group 4 metals (e.g. zirconium, titanium)[3] and zinc,[4] alkali earth metals, e.g., calcium[5] and numerous reports outlining the use of lanthanide complexes have been reported.[6] Much effort has also been expended into the development of catalytic asymmetric hydroamination procedures, especially with rare earth lanthanides.[7]

It is of interest that while intramolecular hydroaminations have been extensively used to synthesise simple *N*-containing heterocycles such as substituted pyrrolidines and piperidines, application to the synthesis of benzo-fused heterocycles has seen little activity. Apart from the synthesis of indoles using a hydroamination approach, only a few examples of the use of this methodology to afford isoquinolines has been reported. Dyker and co-workers reported an interesting approach to dihydroisoquinolines by making use of the Ugi-four component reaction to synthesize **1**. This compound then underwent hydroamination with a gold catalyst to afford compounds of type **2**.[8] A fascinating set of examples reported by Marks and co-workers demonstrated that treatment of the divinylarenes **3** with a lanthanum catalyst afforded 1-methyltetrahydroisoquinolines (1-MeTHIQ) **5** in excellent yields.[9] These products were presumably produced by an intermolecular hydroamination to afford **4** as an intermediate. This was followed by an intramolecular reaction to give compound **5** (Figure 1). Another sequential intramolecular hydroamination published by Molander and Pack, facilitated by a neodymium catalyst, also gave rise to fused THIQs in good yields.[10a]

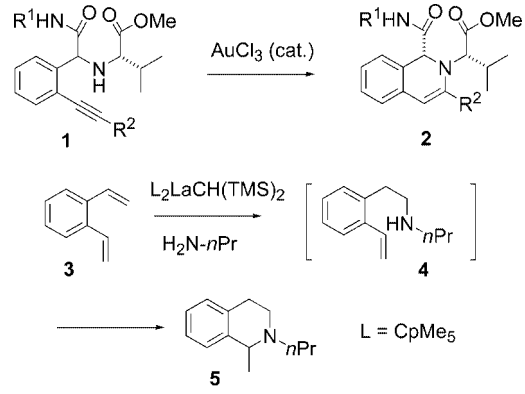

Figure 1. Published approaches to THIQs using hydroamination.

THIQs are of great interest to the synthetic, medicinal and natural products chemistry community. THIQs have found much application in pharmaceutical chemistry due to the interesting biological activities displayed by THIQ-containing molecules in natural and synthetic compounds. Natural products containing the THIQ motif range from the very simple, such as carnegine **6**[11a] and salsolidine **7**,[11b] to compounds with THIQs imbedded in their complex structure (see for instance saframycin A).[12] Examples of medicinally important THIQ compounds with a complex skeleton would include ecteinascidin 743 **9**, a THIQ extracted from a marine tunicate,[13a] which is now in several *anti*-cancer clinical trials.[13b] Finally, 1-MeTHIQ **10** is an example of a simple THIQ which has elicited much interest from the pharmaceutical world (Figure 2).[14]

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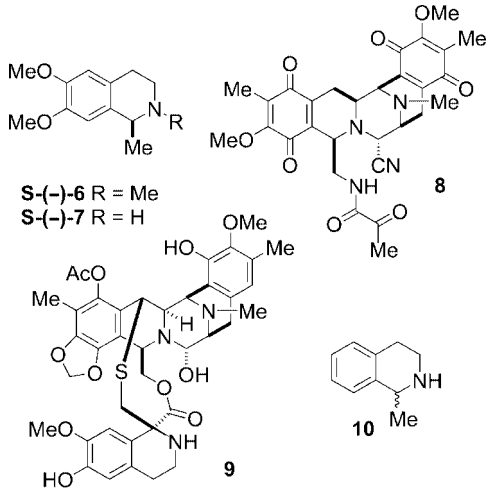


Figure 2. Topical examples of THIQs.

In recent years we have been interested in synthesising analogues of naturally-occurring naphthylisoquinoline alkaloids,[15] e.g. korupensamine B **11** and michellamine B **12**.[16] To this end we published details of a novel mercury-mediated reductive amidation of compounds such as **13** to afford the corresponding *N*-acetyl-1,3-dimethyl-THIQs **14**.[17] In this full paper we describe an extension of this methodology to include the synthesis of 3-methyl-THIQs and 3,4-dimethyl-THIQs **16** (Figure 3) from aromatic aminoalkenes **15** using intramolecular hydroamination reactions.[18] In this paper we will divulge details of a reductive mercuration as well as a *n*-butyllithium-mediated hydroamination approach to the THIQ skeletons.[19]

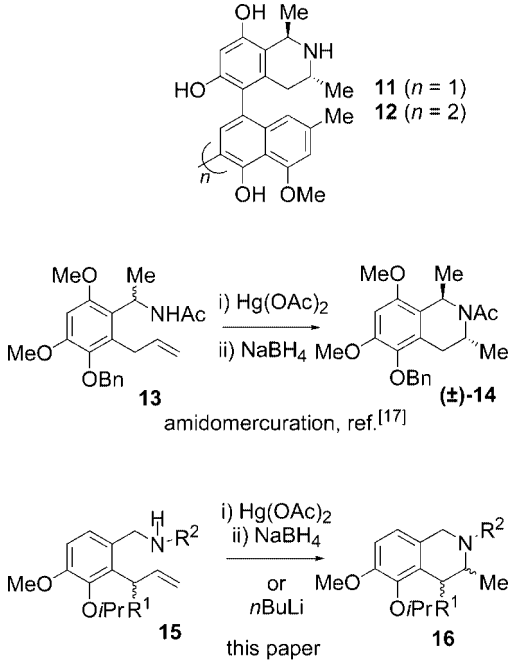
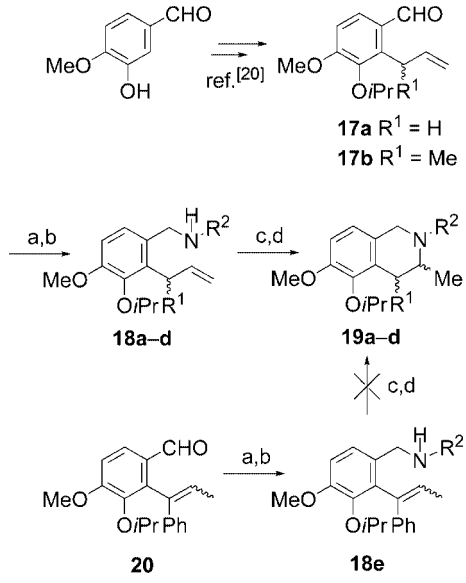


Figure 3. Our group's approaches to substituted THIQs.

Results and Discussion

Hydroamination by a Reductive Mercuration Procedure

The first part of this project involved the synthesis of the *ortho*-allylbenzylamines **18a**–**d** (Scheme 1, Table 1). The substituted benzaldehyde **17** was synthesized as described previously[20] and a subsequent reliable two-step reductive amination procedure then afforded the amines **18a**–**d** in excellent yields. An advantage of this approach was that compounds **18a**–**d** could be obtained in high purity without laborious chromatographic procedures. Finally compounds **18e** was synthesized from compound **20** in a similar manner.



Scheme 1. Reagents and conditions: (a) R^2NH_2, *p*-TSA, benzene or toluene, Dean–Stark apparatus, reflux, 18 h; (b) $NaBH_4$, MeOH, H_2O (1 drop), 0 °C, 1 h (for yields see Table 1); (c) $Hg(OAc)_2$, THF/H_2O (1/1), room temp., 18 h; (d) aq. NaOH, $NaBH_4$, 0 °C to room temp., 18 h (for yields see Table 1).

Table 1. Yields for tetrahydroisoquinolines **19a**–**d** (reductive mercuration procedure).

Entry	R^1	R^2	**17→18**[a]	**18→19**
a	H	Bn	99%	82%
b	H	*n*Pr	99%	90%
c	Me	Bn	92%	63% (2:1 *cis*:*trans*)
d	Me	*n*Pr	97%	86% (2:3 *cis*:*trans*)
			20→18[a]	
e	Ph	*n*Bu	90%	–[b]

[a] Yields over two steps. [b] Only starting material recovered.

The *ortho*-allylated benzylamines **18a**–**e** were then treated with a stoichiometric amount of mercury(II) acetate in a water/THF (1:1) solvent mixture (Scheme 1). Sodium borohydride-mediated reduction of the in situ formed organomercury intermediate under basic conditions then led to the formation of the corresponding THIQs **19a**–**d** in moderate to excellent yields. Both the ^1H and ^{13}C NMR spectra confirmed the formation of the desired THIQ sys-

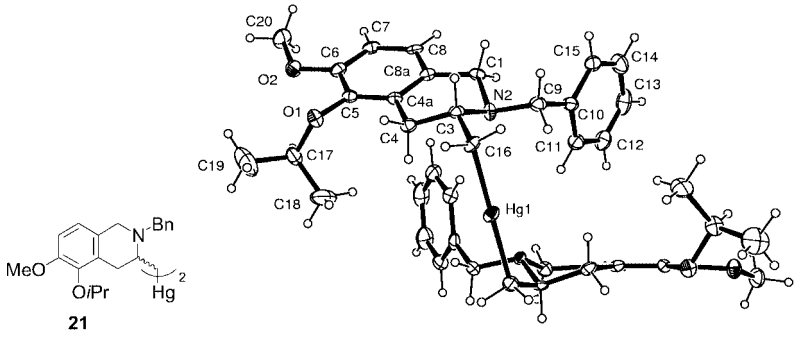


Figure 4. ORTEP diagram of the X-ray crystal structure of compound **21** (ellipsoids shown at 30% probability).

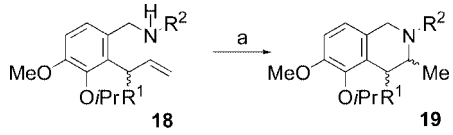
tems. A point of interest is that this approach afforded 3,4-dimethyl compounds **19c** and **19d** in reasonable yields, each as a *cis* and *trans* diasteriomeric mixture. In our hands it was found to be difficult to separate these isomers but careful interpretation of the spectra of compounds **19c** and **19d** after chromatography, allowed us to estimate the *cis*/*trans* ratio of the compounds obtained (see later in this paper for details). A literature search revealed that there are only a few published routes to this type of 3,4-dialkyl-THIQ.[21] Unfortunately, the treatment of the substrate **18e** with the reductive mercuration procedure did not generate the desired THIQ; only unchanged starting material was recovered. The failure of the reaction probably is due to the electron-rich nature of the 1,1-diphenylethene although steric factors could also be important.

An interesting side issue was that when the initial reductive mercuration experiment was performed on **18a** an off-white solid was obtained prior to the sodium borohydride reduction step. A small amount of this material was recrystallised and this compound's structure was determined by single-crystal X-ray crystallography. Quite surprisingly, the crystalline material consisted of the dimeric THIQ-mercury compound **21** (Figure 4). A search of the Cambridge Crystallographic database revealed that there are not many bis-organic mercury complexes known[22] and that compound **21** is one of the most complex compounds of this sort now characterized by crystallography.

The use of stoichiometric amounts of mercury in organic synthesis has obvious disadvantages when taking environmental issues into account. We thus considered the use of hydroaminations mediated by alternative methods, of which there are numerous recent literature examples as shown in the introductory paragraphs of this paper. To us, the work described by several research groups,[23] on the intramolecular transamination of styrenes and allyl aryl compounds with amines, utilizing *n*-butyllithium as a catalyst, seemed the most promising.

Hydroamination Mediated by Sub-Stoichiometric Amounts of *n*-Butyllithium

The *ortho*-allylated benzylamines **18a**–**e**, used previously in the aminomercuration procedure, were thus treated with sub-stoichiometric quantities of *n*-butyllithium at 60 °C (Scheme 2). Satisfyingly, the THIQs **19a**–**d** were obtained in reasonable yields after purification by chromatography and their NMR spectra compared well with the compounds synthesised by the aminomercuration procedure. To the best of our knowledge this represents the first application of this methodology towards the synthesis of THIQs.[18] We also attempted the reaction on substrate **18f**,[24] which contains an additional *N*-allyl functional group, in the hope of achieving a tandem ring-closure but this reaction was unfruitful.[10] Unfortunately, substrate **18e** also failed to give the desired product.



Scheme 2. Reagents and conditions: (a) *n*BuLi (2 × 16 mol-%), room temp., 6 h, then 60 °C, 18 h (for yields see Table 2).

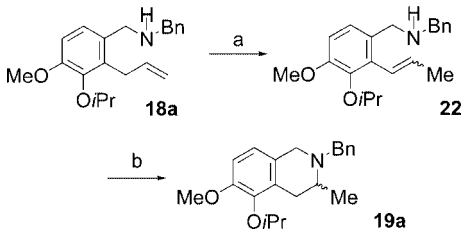
Table 2. Yields for tetrahydroisoquinolines **19a**–**d** (procedure using sub-stoichiometric amounts of *n*-butyllithium).

Entry	R^1	R^2	**18→19**
a	H	Bn	87%
b	H	*n*Pr	65%
c	Me	Bn	63% (5:1 *cis*:*trans*)
d	Me	*n*Pr	62%[b]
e	Ph	*n*Bu	–[a]
f	H	allyl	–[a]

[a] Only starting material recovered. [b] *cis*:*trans* ratio not determined due to impurities in spectrum.

As a consequence we decided to do some preliminary investigation into the mechanistic details of the *n*BuLi-catalysed reaction and found that when similar reaction conditions were employed on substrate **18a**, albeit at room temperature, isomerized compound **22** was isolated in good yield. Subsequent reaction of compound **22** with a sub-stoichiometric amount of *n*-butyllithium at 60 °C gratifyingly affforded the expected THIQ **19a** (Scheme 3). This suggests that the initial step in this reaction involves isomerization of the allyl group to the thermodynamically more stable styrene compound followed by the intramolecular transamination. This proposed mechanism is also sup-

ported by the work of Marks et al.[9] and Molander and Pack,[10] in which styrenes were converted into THIQs by way of intramolecular hydroamination using lanthanide catalysts.



Scheme 3. Reagents and conditions: (a) *n*BuLi (2 × 16 mol-%), room temp., 18 h, 96%; (b) *n*BuLi (16 mol-%), 60 °C, 18 h, NMR spectra identical to that obtained in Scheme 1.

Stereochemical Aspects of the Hydroamination Reactions

The determination of the stereochemical outcomes of the hydroaminations were done by analysis of the NMR spectra of the products **19c** and **19d**. As the crude NMR spectra for the compounds synthesized were often difficult to interpret, careful chromatography was performed before estimation of the *cis*:*trans* ratios. A literature search reveals a modest collection of papers describing the synthesis of 3,4-disubstituted THIQs[25] with only a few authors investigating the stereochemical arrangement of the substituents on the heterocyclic ring.[25a–c] Pedrosa, Andrés and co-workers argue that a coupling constant of zero Hertz between the hydrogens 3-H and 4-H is indicative of a *trans* 3,4-disubstituted THIQ as a dihedral angle of 90° is only possible for a *trans* relationship.[25a] Perusal of the NMR spectroscopic data for a number of *trans*-3,4-disubstituted THIQs described in the literature confirmed that coupling constant for the interaction between the 3-H and 4-H protons was invariably zero Hertz[25b,25c] or very close to it (for example 0.6 Hz).[21a] Unfortunately we were unable to find well characterized examples of 3,4-disubstituted THIQs bearing substituents in a *cis* relationship.

The ^{1}H NMR spectrum of THIQ **19c**, synthesized by both the reductive mercuration and *n*BuLi methods**,** indicated it to contain a mixture of *cis* and *trans* isomers with what appeared to be the *cis* isomer being the major product. This was determined by looking at the coupling constant between the 3-H (dq, J = 3.0 and 6.7 Hz) and 4-H protons (dq, J = 3.0 and 6.6 Hz) of this isomer, which turned out to be 3.0 Hz. Evaluation of the coupling constant for the other isomer proved to be impossible due to overlapping signals in this instance. Due to the paucity of examples which described *cis*-3,4-disubstituted THIQs we decided to see if we could support the existence of the *cis* relationship by way of other NMR spectroscopy techniques. It would not be unreasonable to assume that the 4-C methyl substituent occupies a *pseudo*-axial position due to *peri* interactions with the adjacent isopropyl group and that the 3-C methyl substituent is in an equatorial position (Figure 5). Of interest is that irradiation of 3-H only showed nOe interactions with the 3-C methyl substituent, the 4-H proton and one of the benzylic methylene protons. On the other hand, irradiation at 4-H showed an nOe interaction with the 4-C methyl substituent, 3-H proton and the C-H proton of the isopropyl group. Of importance is that the strong 3-H···4-H interaction supports the *cis*-arrangement of the methyl groups (Figure 5). Of additional interest is that the 3-H and 4-H protons do not show nOe interactions with the methyl substituents on the opposing carbons which would be expected if there was a *trans* relationship. Simple molecular modelling[26] of a model compound also showed a coupling constant of about 3.0 Hz in the case of *cis* hydrogen atoms (torsional angle between 3-H and 4-H of 44–50°), while for *trans* hydrogen atoms a value of about 1.0 Hz was to be expected (torsional angle between 3-H and 4-H of 80–84°). Thus the molecular modelling values were also in agreement with those obtained from the ^{1}H NMR spectrum of *cis*-**19c**.

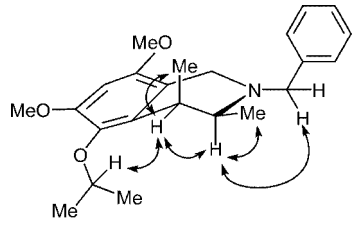
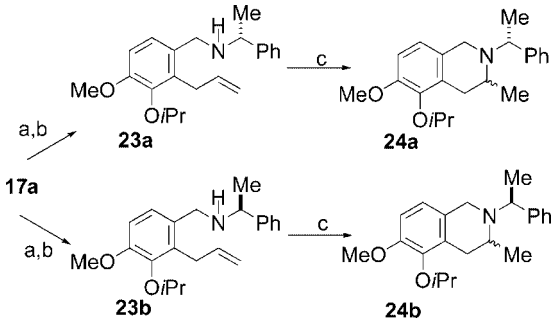


Figure 5. nOe interactions for the *cis*-isomer of **19c**.

The ^{1}H NMR spectrum of compound **19d** proved to be fairly complex in the aliphatic region depicting the methyl groups, as there were ten methyl groups in total. However, the region 2–4 ppm, in the ^{1}H NMR spectrum, proved to be much more informative. It was clear from the ^{1}H NMR spectrum that there were two isomers in a ratio of 2:3, and a doublet of quartets (3.3 and 6.6 Hz) was evident for the minor diastereoisomer. A CH-correlation NMR spectrum allowed us to identify this signal as belonging to 4-H of the minor isomer. Furthermore, a multiplet (δ = 2.85–2.96) contained another two doublet of quartets: one for the minor and major isomer's 3-H protons with coupling constants 3.0 and 6.7 Hz, and 1.9 and 6.6 Hz, respectively. The minor component in the ^{1}H NMR spectrum is probably the *cis*-isomer by direct comparison with the **19c** example. Of interest is that the 3-H and 4-H coupling constant for the *trans*-isomer, although not zero, is smaller at 1.9 Hz. Perhaps it is due to the constraints imposed on the molecule by the *peri* interactions between the 4-CH_3 and the isopropyloxy group which prevents the 90° angle between the methyl groups and the subsequent coupling constant of zero Hertz.

Due to the strong focus on stereoselective syntheses of natural compounds, including the THIQs,[27] we attempted to devise a strategy that would allow for a diastereoselective hydroamination reaction, promoted by *n*-butyllithium. We thus synthesised the amines (*R*)-**23a** and (*S*)-**23b**, both containing the chiral 1-phenylethyl group, from precursor **17a**. This chiral auxiliary has been used recently in the directed

reductions of,[28a] or Grignard addition to,[28b] substituted isoquinolinium salts, with acceptable diastereoselectivities. We thus hoped that this auxiliary would also facially direct attack by the amine onto the styrene intermediate. Compounds (*R*)-**23a** and (*S*)-**23b** were thus individually subjected to sub-stoichiometric amounts of *n*-butyllithium and the reaction products were evaluated by NMR spectroscopy (Scheme 4, Table 3). Evaluation of the ^{1}H NMR spectra of the crude products (1′*R*)-**24a** and (1′*S*)-**24b**, showed disappointingly, that only a mixture of diastereomers with no diastereoselectivity bias had been formed in the hydroamination reaction. In a similar fashion, the use of the reductive mercuration methodology only afforded a diastereomeric mixture. These results then confirmed that the cyclizations involving the chiral benzylamine derivatives were unselective under our hydroamination conditions.



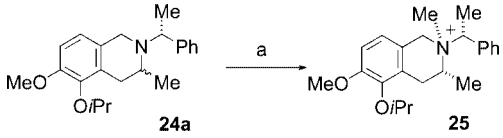
Scheme 4. Reagents and conditions: (a) (*R*)- or (*S*)-1-phenylethylamine, *p*-TSA, benzene or toluene, Dean–Stark apparatus, reflux, 18 h; (b) $NaBH_4$, MeOH, H_2O (1 drop), 0 °C to room temp., 18 h; (c) *n*BuLi (2 × 16 mol-%), room temp., 6 h, then 60 °C, 18 h. For yields see Table 3.

Table 3. Yields for tetrahydroisoquinolines **24a** and **24b** (reductive mercuration and sub-stoichiometric *n*-butyllithium procedure).

Entry	Chiral auxilary	**17**→**23**[a]	$Hg(OAc)_2/NaBH_4$ **23**→**24**	*n*BuLi **23**→**24**
a	(*R*)-CH(Me)Ph	89%	76%	75%
b	(*S*)-CH(Me)Ph	98%	87%	79%

[a] Yields over two steps.

Finally, quaternization of the diastereomeric mixture **24a** with methyl iodide gave a solid from which 3-(1′*R*,3*R*)-**25** was recrystallized from MeOH/EtOAc (Scheme 5). A single-crystal X-ray structural determination was subsequently done to confirm the postulated structure.[18a]



Scheme 5. Reagents and conditions: (a) MeI, recrystallized from MeOH/EtOAc.

Conclusions

In this paper we have thus demonstrated that the hydroamination approach, utilizing either a reductive mercuration or a *n*-butyllithium mediated approach is useful for the synthesis of polysubstituted THIQs. Unfortunately these methodologies did not allow for the stereospecific synthesis of the THIQ compounds by utilizing a chiral auxiliary. However, we will continue to evaluate hydroamination reactions as ways of synthesizing interesting THIQs and these investigations will be divulged in due course.

Experimental Section

General Remarks: The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200 (200.13 MHz), Bruker AVANCE 300 (300.13MHz) or Bruker DRX 400 (400.13 MHz) spectrometer at the frequency indicated. The chemical shifts are reported in parts per million (ppm) with TMS as the internal standard in the ^{1}H NMR spectra and using δ = 77.00 ($CDCl_3$) as reference peak in the ^{13}C NMR spectra. ^{1}H and ^{13}C NMR spectroscopic assignments with the same superscript are interchangeable. IR spectra were recorded on a Bruker IFS-25 Fourier Transform spectrometer or on a Bruker Vector-22 Fourier Transform spectrometer (liquid samples: NaCl plates, solid samples: KBr plates). High resolution mass spectra (HRMS) were recorded on a VG70 MS (Mass Spectrum CC Pyramid data system) or on a VG70 SEQ (VG 11-250J or Marc II data systems). Optical rotations were determined on a Jasco DIP 3-70 instrument at 22 °C at the sodium D line. $[\alpha]_D$ values are given in 10^{-1} deg·cm^2·g^{-1}. The melting points were determined on a Reichert hot-stage microscope and are uncorrected. For the silica gel chromatography Macherey–Nagel Kieselgel 60 (particle size 0.063–2.00 mm) was used. Aluminium-backed Macherey–Nagel ALUGRAM Sil G/UV_{254} was used for thin layer chromatography (TLC). All the solvents used for reactions and chromatography were distilled prior to use according to the standard procedures.[29]

Representative Procedure for the Preparation of Substituted Amines 18: Aldehyde **17** (ca. 1 g, ca. 4 mmol), the amine (ca. 3 mol equiv.) and *p*-TSA (ca. 0.1 mol equiv.) were dissolved in benzene (50 cm^3) and were heated at reflux, with stirring, using a Dean–Stark head under N_2 for 24 h. On completion of the reaction (monitored by TLC) the benzene was evaporated under reduced pressure. The resulting material was diluted with CH_2Cl_2 (30 cm^3) and washed with aqueous saturated $NaHCO_3$ (30 cm^3). The organic layer was then dried ($MgSO_4$) to obtain the imine in reasonably pure form. The residue was then dissolved in MeOH (10 cm^3) and cooled to 0 °C over ice. To this solution, $NaBH_4$ (ca. 1.2 mol equiv.) was added together with a drop of H_2O and the mixture was stirred for one hour at 0 °C. On completion of the reaction, the MeOH was removed under reduced pressure. The residue was diluted with EtOAc (30 cm^3) and washed with H_2O (2 × 30 cm^3). The organic layer was then separated and dried ($MgSO_4$). The solvent was then removed under reduced pressure to afford amine **18** as a yellow oil, in yields of 89% to quantitative. The amines **18** were used without any further purification in the next reaction.

***N*-[(2-Allyl-3-isopropoxy-4-methoxyphenyl)methyl]benzylamine (18a):** This product was isolated as a yellow oil (1.39 g, 99%), starting from aldehyde **17a** (1.01 g, 4.27 mmol) and benzylamine. IR (film): $\tilde{\nu}_{max}$ = 3322, 3062, 2974, 2835, 1637, 1600, 1580, 1487, 1437, 1380, 1271 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 [d, *J* = 6.2 Hz, 6 H, $CH(CH_3)_2$], 1.56 (br. s, 1 H, NH), 3.51 (br. d, *J* = 5.8 Hz, 2 H, $ArCH_2CH$), 3.75 (s, 2 H, $ArCH_2N$),[a] 3.79–3.84 (m, 2 H, $NHCH_2Ph$),[a] 3.80 (s, 3 H, OCH_3), 4.50 [sept, *J* = 6.2 Hz, 1 H, $CH(CH_3)_2$], 4.80–4.94 (m, 2 H, $CH=CH_2$), 5.86–5.95 (m, 1 H, $CH=CH_2$), 6.74 (d, *J* = 8.4 Hz, 1 H, ArH), 7.02 (d, *J* = 8.4 Hz, 1 H,

ArH) and 7.22–7.33 (m, 5 H, 5×ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.6 [CH(*C*H$_3$)$_2$], 30.7 (Ar*C*H$_2$CH), 50.5 (Ar*C*H$_2$NH),[b] 53.5 (NH*C*H$_2$Ph),[b] 55.5 (OCH$_3$), 74.4 [*C*H(CH$_3$)$_2$], 109.9 (CH), 114.6 (CH), 124.1 (CH), 126.8 (CH), 128.2 (2 × CH), 128.3 (2×CH), 131.6 (C), 132.6 (C), 137.3 (CH), 140.4 (C), 145.1 (C), 151.8 (C) ppm. MS: *m*/*z* 325 (M$^+$, 15%), 234 (29), 218 (23), 177 (36), 176 (100), 161 (38), 91 (96). HRMS: calcd. for $C_{21}H_{27}NO_2$: 325.2042, found: 325.2050.

***N*-[(2-Allyl-3-isopropoxy-4-methoxyphenyl)methyl]propylamine (18b):** This product was isolated as a yellow oil (1.18 g, 99%), starting from aldehyde **17a** (1.01 g, 4.31 mmol) and *n*-propylamine. IR (film): $\tilde{\nu}_{max}$ = 2972, 2835, 1637, 1600, 1487, 1438, 1380, 1273 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.4 Hz, 3 H, CH$_3$), 1.18 [d, *J* = 6.2 Hz, 6 H, CH(C*H*$_3$)$_2$], 1.37–1.49 (m, 2 H, C*H*$_2$CH$_3$), 2.51 (t, *J* = 7.2 Hz, 2 H, NHC*H*$_2$CH$_2$), 3.46–3.47 (m, 2 H, ArC*H*$_2$-CH),[a] 3.61 (s, 2 H, ArC*H*$_2$N),[a] 3.73 (s, 3 H, OCH$_3$), 4.43 [sept, *J* = 6.2 Hz, 1 H, C*H*(CH$_3$)$_2$], 4.81–4.91 (m, 2 H, CH=C*H*$_2$), 5.81–5.94 (m, 1 H, C*H*=CH$_2$), 6.67 (d, *J* = 8.4 Hz, 1 H, ArH), 6.92 (d, *J* = 8.4 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.8 (CH$_3$), 22.5 [CH(*C*H$_3$)$_2$], 23.1 (*C*H$_2$CH$_3$), 30.7 (Ar*C*H$_2$CH), 51.2 (ArCH$_2$N),[b] 51.6 (NH*C*H$_2$CH$_2$),[b] 55.5 (OCH$_3$), 74.3 [*C*H(CH$_3$)$_2$], 109.9 (CH), 114.5 (CH), 123.9 (CH), 132.0 (C), 132.3 (C), 137.4 (CH), 145.0 (C), 151.7 (C) ppm. MS: *m*/*z* 276 (M$^+$, 85%), 177 (76), 176 (100), 161 (31), 147 (28). HRMS: calcd. for $C_{17}H_{26}NO_2$ (M$^+$ – H): 276.1964, found: 276.1964.

***N*-{[3-Isopropoxy-4-methoxy-2-(1-methylprop-2-en-1-yl)phenyl]-methyl}benzylamine (18c):** This product was isolated as a yellow oil (0.445 g, 92%), starting from aldehyde **17b** (0.35 g, 1.42 mmol) and benzylamine. IR (film): $\tilde{\nu}_{max}$ = 2975, 2935, 2836, 1632, 1598, 1484, 1453, 1439, 1381, 1284 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 [d, *J* = 6.2 Hz, 3 H, CH(CH$_3$)C*H*$_3$], 1.27 [d, *J* = 6.2 Hz, 3 H, CH(C*H*$_3$)CH$_3$], 1.36 (d, *J* = 7.2 Hz, 3 H, CHCH$_3$), 1.40–1.50 (br. s, 1 H, NH), 3.67–3.80 (m, 2 H, ArC*H*$_2$N),[a] 3.80 (s, 3 H, OCH$_3$), 3.87 (s, 2 H, NHC*H*$_2$Ph),[a] 4.27–4.31 [m, 1 H, ArC*H*(CH$_3$)], 4.57 [sept, *J* = 6.2 Hz, 1 H, C*H*(CH$_3$)$_2$], 4.92–4.99 (m, 2 H, CH=C*H*$_2$), 6.08–6.16 (m, 1 H, C*H*=CH$_2$), 6.75 (d, *J* = 8.4 Hz, 1 H, ArH), 7.09 (d, *J* = 8.4 Hz, 1 H, ArH), 7.22–7.36 (m, 5 H, 5×ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7 [ArCH(*C*H$_3$)], 22.4 and 22.5 [CH(*C*H$_3$)$_2$], 34.4 [Ar*C*H(CH$_3$)], 50.4 (ArCH$_2$N),[b] 53.7 (NH*C*H$_2$Ph),[b] 55.5 (OCH$_3$), 74.0 [*C*H(CH$_3$)$_2$], 110.0 (CH), 112.3 (CH), 124.9 (CH), 126.4 (C), 126.7 (CH), 127.7 (2×CH), 128.2 (2×CH), 131.8 (C), 137.7 (C), 140.5 (C), 143.2 (CH), 151.5 (C) ppm. MS: *m*/*z* 339 (M$^+$, 13%), 296 (7), 248 (46), 191 (42), 190 (100), 175 (61). HRMS: calcd. for $C_{22}H_{29}NO_2$: 339.2198, found: 339.2196.

***N*-{[3-Isopropoxy-4-methoxy-2-(1-methylprop-2-en-1-yl)phenyl]-methyl}propylamine (18d):** This product was isolated as a yellow oil (1.14 g, 97%) starting from aldehyde **17b** (1.00 g, 4.03 mmol) and *n*-propylamine. IR (film): $\tilde{\nu}_{max}$ = 3079, 2979, 2934, 2873, 1633, 1598, 1577, 1485, 1381, 1376, 1274 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, no signal observed for NH): δ = 0.92 (t, *J* = 7.2 Hz, 3 H, CH$_2$CH$_3$), 1.24 [d, *J* = 6.2 Hz, 3 H, CH(C*H*$_3$)CH$_3$], 1.27 [d, *J* = 6.2 Hz, 3 H, CH(C*H*$_3$)CH$_3$], 1.40 [d, *J* = 7.2 Hz, 3 H, ArCH(C*H*$_3$)], 1.45–1.55 (m, 2 H, C*H*$_2$CH$_3$), 2.58 (t, *J* = 7.2 Hz, 2 H, NHC*H*$_2$CH$_2$), 3.63–3.74 (m, 2 H, ArC*H*$_2$NH), 3.80 (s, 3 H, OCH$_3$), 4.28–4.34 [m, 1 H, ArC*H*(CH$_3$)], 4.57 [sept, *J* = 6.2 Hz, 1 H, CH(CH$_3$)$_2$], 4.98–5.04 (m, 2 H, CH=C*H*$_2$), 6.11–6.22 (m, 1 H, C*H*=CH$_2$), 6.75 (d, *J* = 8.4 Hz, 1 H, ArH), 7.06 (d, *J* = 8.4 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.8 (CH$_3$), 18.8 (*C*H$_2$CH$_3$), 22.5 and 22.6 [CH(*C*H$_3$)$_2$], 23.2 (ArCH*C*H$_3$), 34.5 (Ar*C*HCH$_3$), 51.0 (Ar*C*H$_2$N),[a] 51.8 (NH*C*H$_2$CH$_2$),[a] 55.5 (OCH$_3$), 74.1 [*C*H(CH$_3$)$_2$], 110.1 (CH), 112.4 (CH), 124.9 (CH), 132.1 (C), 137.6 (C), 143.4 (CH), 144.4 (C), 151.5 (C) ppm. MS: *m*/*z* 291 (M$^+$, 46%), 248 (77), 206 (26), 176 (34), 143 (100), 115 (27), 91 (22), 43 (42). HRMS: calcd. for $C_{18}H_{29}NO_2$: 291.2194, found: 291.2198.

***N*-{[4-Methoxy-2-(1-phenylprop-1-enyl)-3-propoxyphenyl]-methyl}butylamine (18e):** This product was isolated as a orange-brown oil (0.46 g, 90%), starting from aldehyde **20** (0.43 g, 1.39 mmol) and *n*-butylamine. IR (film): $\tilde{\nu}_{max}$ = 2955, 1588, 1446, 1271 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.70 (t, *J* = 7.2 Hz, 3 H, CH$_2$C*H*$_3$), 1.06 [d, *J* = 6.1 Hz, 3 H, CH(C*H*$_3$)CH$_3$], 1.11 [d, *J* = 6.1 Hz, 3 H, CH(CH$_3$)C*H*$_3$], 1.20–1.53 (m, 4 H, 2×CH$_2$), 1.62 (d, *J* = 6.9 Hz, 3 H, C=CHC*H*$_3$), 2.04 (s, 1 H, NH), 2.22–2.50 (m, 2 H, NHC*H*$_2$CH$_2$), 3.75–3.95 (m, 5 H, OCH$_3$ and ArC*H*$_2$NH), 4.22–4.30 [m, 1 H, C*H*(CH$_3$)$_2$], 6.50 (q, *J* = 6.9 Hz, 1 H, C=CHCH$_3$), 6.99 (d, *J* = 8.5 Hz, 1 H, ArH), 7.20–7.30 (m, 5 H, 5×ArH), 7.70 (d, *J* = 8.5 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.3 (CH$_3$), 16.2 (CH$_3$), 19.8 (CH$_2$), 22.4 [CH(*C*H$_3$)-CH$_3$], 22.7 [CH(*C*H$_3$)CH$_3$], 28.0 (CH$_2$), 45.9 (NH*C*H$_2$CH$_2$),[a] 47.2 (ArCH$_2$NH),[a] 55.5 (OCH$_3$), 75.1 [*C*H(CH$_3$)$_2$], 111.9 (CH), 125.5 (C), 125.8 (2×CH), 126.5 (CH), 127.2 (CH), 128.3 (CH), 128.6 (2×CH), 134.4 (C), 135.7 (C), 140.3 (C), 145.0 (C), 153.7 (C) ppm. MS: *m*/*z* 367 (M$^+$, 91%), 368 (27), 352 (19), 324 (35), 310 (30), 253 (61), 252 (100), 237 (24), 225 (18), 213 (18), 165 (23), 91 (22). HRMS: calcd. for $C_{24}H_{33}NO_2$: 367.2511, found: 367.2510.

(1*R*)-*N*-[(2-allyl-3-isopropoxy-4-methoxyphenyl)methyl]-(1-phenylethyl)amine (23a): This product was isolated as a yellow oil (0.644 g, 89%), starting from aldehyde **17a** (0.50 g, 2.13 mmol) and (*R*)-(+)-α-methylbenzylamine. $[\alpha]_D^{25}$ = +26.0 (*c* = 1.00, $CHCl_3$); see below **23b** for characterization details.

(1*S*)-23b: This compound was isolated as a yellow oil (0.710 g, 98%), starting from aldehyde **17a** (0.50 g, 2.13 mmol) and (*S*)-(–)-α-methylbenzylamine. $[\alpha]_D^{25}$ = –25.3 (*c* = 0.83, $CHCl_3$). IR (film): $\tilde{\nu}_{max}$ = 2975, 1637, 1601, 1487, 1435, 1370, 1271 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, no signal observed for NH): δ = 1.25 [d, *J* = 6.2 Hz, 6 H, CH(CH$_3$)$_2$], 1.34 (d, *J* = 6.6 Hz, 3 H, CH$_3$), 3.44–3.46 (m, 2 H, ArCH$_2$CH), 3.52 (distorted AB system, 2 H, *J* ≈ 6 Hz, ArCH$_2$NH), 3.77–3.82 [s and m, 4 H, OCH$_3$ and NHCH(CH$_3$)], 4.49 [sept, *J* = 6.2 Hz, 1 H, CH(CH$_3$)$_2$], 4.77 [br. d, *J* = 17.1 Hz, 1 H, CH=C(H)H], 4.87 [dd, *J* = 10.2 and 1.3 Hz, 1 H, CH=C(H)H], 5.82–5.92 (m, 1 H, CH=CH$_2$), 6.73 (d, *J* = 8.4 Hz, 1 H, ArH), 6.95 (d, *J* = 8.4 Hz, 1 H, ArH), 7.24–7.26 (m, 1 H, ArH), 7.22–7.28 (m, 4 H, 4×ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.7 [CH(CH$_3$)$_2$], 24.4 (ArCH$_2$CH), 30.7 (CH$_3$), 49.3 (ArCH$_2$N)[b], 55.6 (OCH$_3$), 58.1 [NHCH(CH$_3$)][b], 74.4 [CH(CH$_3$)$_2$], 110.0 (CH), 114.5 (CH), 124.3 (CH), 126.8 (2×CH), 126.9 (CH), 128.4 (2×CH), 132.0 (C), 132.6 (C), 137.5 (CH), 145.1 (C), 145.7 (C), 151.8 (C) ppm. MS: *m*/*z* 339 (M$^+$, 22%), 248 (60), 218 (42), 177 (88), 161 (60), 144 (40), 17 (52), 105 (100), 77 (42). HRMS: calcd. for $C_{22}H_{29}NO_2$: 339.2198, found: 339.2198.

Representative Procedure for Preparing Substituted 5-Isopropoxy-6-methoxy-1,2,3,4-tetrahydroisoquinolines 19. Reductive Mercuration Procedure: Hg(OAc)$_2$ (1.1 mol equiv.) was added to amine **18** (0.3–0.7 mmol) dissolved in a solution of THF (10 cm^3) and H$_2$O (10 cm^3), and the reaction mixture was stirred at room temp. for 24 h. NaOH solution (3 M, 5 cm^3) was then added and the mixture was stirred for a further 20 min. A solution of NaBH$_4$ (1.1 mol equiv.) in NaOH (3 M, 5 cm^3) was then added and the reaction mixture was then stirred for 24h at room temp. After standing for 30 min the mixture was decanted and filtered twice through Celite. H$_2$O (30 cm^3) was added and the mixture was extracted with Et$_2$O (3×10 cm^3). The organic phase was dried (MgSO$_4$) and then evaporated under reduced pressure to obtain the crude residue. This was purified by column chromatography (10% MeOH/CH$_2$Cl$_2$) to

afford 5-isopropoxy-6-methoxy-1,2,3,4-tetrahydroisoquinolines **19** as oils.

2-Benzyl-5-isopropoxy-6-methoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (19a): This product was isolated as a yellow oil (0.082 g, 82%), starting from amine **18a** (0.10 g, 0.31 mmol). IR (film): $\tilde{\nu}_{max}$ = 1645, 1575, 1277 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.13 (d, J = 6.5 Hz, 3 H, $CHCH_3$), 1.28 [d, J = 6.1 Hz, 3 H, $CH(CH_3)$-CH_3], 1.29 [d, J = 6.1 Hz, 3 H, $CH(CH_3)CH_3$], 2.64 (dd, J = 5.9 and 16.9 Hz, 1 H, 4-H_{eq}), 2.91 (dd, J = 4.9 and 16.9 Hz, 1 H, 4 H_{ax}), 3.04–3.10 (m, 1 H, 3-H), 3.48–3.81 (m, 4 H, 1-H and NCH_2Ph), 3.80 (s, 3 H, OCH_3), 4.48 [sept, J = 6.2 Hz, 1 H, $CH(CH_3)_2$], 6.64 (d, J = 8.4 Hz, 1 H, ArH), 6.71 (d, J = 8.4 Hz, 1 H, ArH), 7.22–7.38 (m, 5 H, 5 × ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 1 C signal not observed in aromatic region of spectrum): δ = 15.0 (CH_3), 22.6 and 22.7 [$CH(CH_3)_2$], 30.8 (4-C), 51.0 (1-C),[a] 51.7 (NCH_2Ph),[a] 55.7 (3-C), 57.2 (OCH_3), 74.1 [$CH(CH_3)_2$], 110.2 (CH), 121.0 (CH), 126.7 (CH), 127.5 (C), 128.4 (2 × CH), 128.8 (2 × CH), 139.3 (C), 144.6 (C), 150.6 (C) ppm. MS: m/z 325 (M^+, 64%), 310 (100), 266 (37), 192 (72), 176 (41), 150 (99), 149 (64), 91 (55). HRMS: calcd. for $C_{21}H_{27}NO_2$: 325.2042, found: 325.2042.

5-Isopropoxy-6-methoxy-3-methyl-2-propyl-1,2,3,4-tetrahydroisoquinoline (19b): This product was isolated as a yellow oil (0.18 g, 90%), starting from amine **18b** (0.20 g, 0.72 mmol). IR (film): $\tilde{\nu}_{max}$ = 1646, 1599, 1473, 1449, 1377, 1278 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, J = 7.4 Hz, 3 H, $NCH_2CH_2CH_3$), 1.07 (d, J = 6.5 Hz, 3 H, $CHCH_3$), 1.26 [d, J = 6.2 Hz, 3 H, $CH(CH_3)CH_3$], 1.27 [d, J = 6.2 Hz, 3 H, $CH(CH_3)CH_3$], 1.54–1.59 (m, 2 H, NCH_2CH_2), 2.38–2.45 [m, 1 H, NC(*H*)HCH_2], 2.53–2.63 [m, 2 H, NC(H)*H*CH_2 and 4-H_{ax}], 2.88 (dd, J = 4.9 and 16.9 Hz, 1 H, 4 H_{eq}), 2.95–3.00 (m, 1 H, 3-H), 3.62–3.75 (m, 2 H, 1-H), 3.80 (s, 3 H, OCH_3), 4.47 [br. sept, J = 6.2 Hz, 1 H, $CH(CH_3)_2$], 6.72 (s, 2 H, 2 × ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.0 ($NCH_2CH_2CH_3$), 15.4 ($CHCH_3$), 20.4 (NCH_2CH_2), 22.6 and 22.7 [$CH(CH_3)_2$], 31.1 (4-C), 51.6 (NCH_2CH_2),[a] 51.9 (1-C),[a] 54.9 (3-C),[a] 55.8 (OCH_3), 74.1 [$CH(CH_3)_2$], 110.2 (CH), 121.0 (CH), 127.8 (C), 129.0 (C), 144.6 (C), 150.7 (C) ppm. MS: m/z 277 (M^+, 47%), 276 (26), 262 (97), 248 (100), 150 (42), 43 (75). HRMS: calcd. for $C_{17}H_{27}NO_2$: 277.2042, found: 277.2042.

(±)-2-Benzyl-5-isopropoxy-6-methoxy-3,4-*cis*-dimethyl-1,2,3,4-tetrahydroisoquinoline and (±)-2-benzyl-5-isopropoxy-6-methoxy-3,4-*trans*-dimethyl-1,2,3,4-tetrahydroisoquinoline (19c): This product was isolated as a yellow oil (0.126 g, 63%) (2:1 *cis*:*trans*), starting from amine **18c** (0.20 g, 0.59 mmol). IR (film): $\tilde{\nu}_{max}$ = 1648, 1600, 1494, 1435, 1381, 1368, 1281 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, signals observed for *cis* isomer): δ = 1.18 (d, J = 6.2 Hz, 3 H, $CHCH_3$), 1.23–1.27 [m, 6 H, $CH(CH_3)_2$], 1.38 (d, J = 6.1 Hz, 3 H, $CHCH_3$), 2.78 (dq, J = 3.0 and 6.6 Hz, 1 H, 4-H), 3.03 (dq, J = 3.0 and 6.6 Hz, 1 H, 3-H),[a] 3.11 [d, J = 13.2 Hz, 1 H, ArC(*H*)-HN],[a] 3.18 [d, J = 15.0 Hz, 1 H, NC(H)*H*Ph],[a] 3.72–3.80 [m under OCH_3, 1 H, NC(*H*)HPh],[b] 3.78 (s, 3 H, OCH_3), 4.22 [d, J = 13.2 Hz, 1 H, ArC(*H*)HN],[b] 4.56 [sept, J = 6.2 Hz, 1 H, C*H*-$(CH_3)_2$], 6.55 (d, J = 8.4 Hz, 1 H, ArH), 6.67 (d, J = 8.4 Hz, 1 H, ArH), 7.20–7.32 (m, 3 H, 3 × ArH), 7.39–7.41 (m, 2 H, 2 × ArH); (300 MHz, $CDCl_3$, signals observed for *trans* isomer, not all protons accounted for): δ = 0.90 (d, J = 6.6 Hz, 3 H, $CHCH_3$), 2.90–2.94 (m,2 H, 3-H and 4-H), 3.45 [br. d, J = 15.0 Hz, 1 H, C(*H*)-H], 3.79 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, signals observed for *cis* isomer): δ = 14.9 ($CHCH_3$), 17.9 ($CHCH_3$), 22.3 [$CH(CH_3)_2$], 23.1 (4-C)[c], 36.2 (3-C)[c], 55.8 (OCH_3), 57.4 (1-C)[d], 57.7 (NCH_2Ph)[d], 74.1 [$CH(CH_3)_2$], 110.3 (CH), 120.6 (CH), 126.6 (CH), 128.2 (2 × CH), 128.5 (2 × CH), 134.1 (C), 136.4 (C), 140.6 (C), 143.7 (C), 150.5 (C); (75 MHz, $CDCl_3$, signals observed for *trans* isomer, not all carbon atoms accounted for): δ = 9.9 ($CHCH_3$), 21.5 and 22.1 [$CH(CH_3)_2$], 49.0 (CH_2), 55.7 (OCH_3),[e] 57.4 (1-C),[e] 59.4 (3-C),[e] 74.3 [$CH(CH_3)_2$], 110.0 (CH), 120.8 (CH), 128.7 (CH), 139.7 (C), 144.9 (C), 150.6 (C) ppm. MS: m/z 339 (M^+, 36%), 325 (33), 324 (89), 206 (55), 164 (94), 91 (100), 43 (61). HRMS: calcd. for $C_{22}H_{29}NO_2$: 339.2198, found: 339.2200.

(±)-5-Isopropoxy-6-methoxy-3,4-*cis*-dimethyl-2-propyl-1,2,3,4-tetrahydroisoquinoline and (±)-5-Isopropoxy-6-methoxy-3,4-*trans*-dimethyl-2-propyl-1,2,3,4-tetrahydroisoquinoline (19d): This product was isolated as a yellow oil (0.086 g, 86%) (2:3 *cis*:*trans*), starting from amine **18d** (0.10 g, 0.34 mmol). IR (film): $\tilde{\nu}_{max}$ = 1647, 1597, 1493, 1465, 1439, 1380, 1278 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, signals observed for *cis* isomer): δ = 0.84 (d, J = 6.6 Hz, 3 H, $ArCHCH_3$), 0.91 (t, J = 7.4 Hz, 3 H, $NCH_2CH_2CH_3$), 1.12–1.17 [m, 6 H, $CH(CH_3)_2$], 1.37 (d, J = 6.0 Hz, 3 H, $NCHCH_3$), 1.50–1.57 (m, 2 H, $NCH_2CH_2CH_3$), 2.24 [dt, J = 12.4 and 6.9 Hz, 1 H, NC(*H*)HCH_2CH_3], 2.60 (dq, J = 3.3 and 6.6 Hz, 1 H, 4-H), 2.75 [dt, J = 12.4 and 8.0 Hz, 1 H, NC(H)*H*CH_2CH_3], 2.85–2.95 (m, 1 H, 3-H), 3.32 [d, J = 14.9 Hz, 1 H, ArC(*H*)HN], 3.79 (s, 3 H, OCH_3), 3.95 [d, J = 14.9 Hz, 1 H, ArC(H)*H*N], 4.54–4.58 [m, 1 H, $CH(CH_3)_2$], 6.71 (br. s, 2 H, 2 × ArH); (300 MHz, $CDCl_3$, signals observed for *trans* isomer): δ = 0.94 (t, J = 7.3 Hz, 3 H, $NCH_2CH_2CH_3$), 1.12–1.17 [m, 6 H, $CH(CH_3)_2$], 1.28 (d, J = 6.7 Hz, 3 H, $ArCHCH_3$), 1.37 (d, J = 6.0 Hz, 3 H, $NCHCH_3$), 1.50–1.57 (m, 2 H, $NCH_2CH_2CH_3$), 2.47 (t, J = 7.2 Hz, 2 H, $NCH_2CH_2CH_3$), 2.85–2.95 (m, 2 H, 3-H and 4-H), 3.42 [d, J = 15.1 Hz, 1 H, ArC(*H*)HN], 3.72 [d, J = 15.1 Hz, 1 H, ArC(H)*H*N], 3.80 (s, 3 H, OCH_3), 4.54–4.58 [m, 1 H, $CH(CH_3)_2$], 6.71 (br. s, 2 H, 2 × ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, signals observed for *cis* isomer): δ = 9.9 (CH_3), 14.8 (CH_3), 17.3 (CH_3), 19.6 (CH_2), 22.3 (CH_3), 23.0 (CH_3), 35.9 (4-C), 54.8 (1-C), 55.0 (NCH_2), 55.8 (OCH_3), 56.8 (3-C), 74.1 [$CH(CH_3)_2$], 110.3 (CH), 120.7 (CH), 127.9 (C), 136.5 (C), 143.8 (C), 150.5 (C); (75 MHz, $CDCl_3$, signals observed for *trans* isomer): δ = 11.9 (CH_3), 11.9 (CH_3), 20.8 (CH_2), 21.4 (CH_3), 22.2 (CH_3), 23.1 (CH_3), 36.1 (4-C), 49.5 (1-C), 55.7 (OCH_3), 56.5 (NCH_2), 56.9 (3-C), 73.9 [$CH(CH_3)_2$], 110.0 (CH), 120.8 (CH), 127.4 (C), 134.3 (C), 144.9 (C), 150.6 (C) ppm. MS: m/z 291 (M^+, 56%), 276 (100), 262 (78), 248 (31), 206 (51), 164 (99). HRMS: calcd. for $C_{18}H_{29}NO_2$: 291.2198, found: 291.2199.

5-Isopropoxy-6-methoxy-3-methyl-2-[(1*R*)-1-phenylethyl]-1,2,3,4-tetrahydroisoquinoline (24a): This product was isolated as a yellow oil (0.152 g, 76%) (1:1 diastereoisomeric mixture), starting from amine **23a** (0.20 g, 0.59 mmol). After chromatography the diastereoisomers were obtained in a 4:1 ratio with the major product's data being reported below (the minor diasteriosiomer was epimeric to that reported for **24b** in the next experiment). IR (film): $\tilde{\nu}_{max}$ = 1668, 1601, 1493, 1440, 1369, 1338, 1278 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.84 (d, J = 6.6 Hz, 3 H, CH_3), 1.22 [d, J = 6.2 Hz, 3 H, $CH(CH_3)CH_3$], 1.24 [d, J = 6.2 Hz, 3 H, $CH(CH_3)$-CH_3], 1.40 [d, J = 6.6 Hz, 3 H, $NCH(CH_3)Ph$], 2.62 (dd, J = 16.7 and 2.0 Hz, 1 H, 4-H_{eq}), 2.76 (dd, J = 16.7 and 5.3 Hz, 1 H, 4-H_{ax}), 3.10–3.17 (m, 1 H, 3-H), 3.58 [d, J = 15.2 Hz, 1 H, ArC(*H*)-HN], 3.65 [q, J = 6.6 Hz, 1 H, NC*H*(CH_3)Ar], 3.81 (s, 3 H, OCH_3), 4.01 [d, J = 15.2 Hz, 1 H, ArC(H)*H*N], 4.43 [sept, J = 6.2 Hz, 1 H, $CH(CH_3)_2$], 6.75 (br. s, 2 H, 2 × ArH), 7.20–7.41 (m, 5 H, 5 × ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.4 ($CHCH_3$), 22.4 and 22.5 [$CH(CH_3)_2$], 22.9 ($CHCH_3$), 30.9 (4-C), 46.5 (1-C),[a] 47.3 ($NCHCH_3$),[a] 55.8 (OCH_3), 61.0 (3-C), 74.2 [$CH(CH_3)_2$], 110.2 (CH), 121.3 (CH), 126.8 (CH), 127.2 (2 × CH), 127.8 (C), 128.4 (2 × CH), 128.8 (C), 145.1 (C), 145.9 (C), 150.7 (C) ppm. MS: m/z 339 (M^+, 19%), 324 (81), 166 (34), 148 (26), 105 (100), 43 (43). HRMS: calcd. for $C_{22}H_{29}NO_2$: 339.2198, found: 339.2198.

5-Isopropoxy-6-methoxy-3-methyl-2-[(1*S*)-1-phenylethyl]-1,2,3,4-tetrahydroisoquinoline (24b): This product was isolated as a yellow oil (0.174 g, 87%) (1:1 diastereoisomeric mixture), starting from amine **6d** (0.20 g, 0.59 mmol). After chromatography the diastereoisomers were obtained in a 3:2 ratio with the major product's data being reported below. (the minor diasteriosiomer was epimeric to that reported for **24a** in the previous experiment). IR (film): $\tilde{\nu}_{max}$ = 1665, 1600, 1493, 1451, 1371, 1314, 1278 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.00 (d, J = 6.6 Hz, 3 H, CHCH_3), 1.27 [d, J = 6.2 Hz, 3 H, CH(CH_3)CH$_3$], 1.30 [d, J = 6.3 Hz, 3 H, CH(CH$_3$)CH_3], 1.36 [d, J = 6.6 Hz, 3 H, NCH(CH_3)Ph], 2.71 (dd, J = 3.3 and 16.7 Hz, 1 H, 4-H_{eq}), 2.95 (dd, J = 5.3 and 16.7 Hz, 1 H, 4-H_{ax}), 3.39–3.59 (m, 3 H, 1-H and 3-H[a]), 3.68 (q, J = 6.6 Hz, 1 H, NCH(CH$_3$)],[a] 3.77 (s, 3 H, OCH$_3$), 4.45 [sept, J = 6.2 Hz, 1 H, CH(CH$_3$)$_2$], 6.56 (d, J = 8.4 Hz, 1 H, ArH), 6.66 (d, J = 8.4 Hz, 1 H, ArH), 7.19–7.41 (m, 5 H, 5 × ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.9 (CHCH$_3$), 19.7 [NCH(*C*H$_3$)Ph], 22.6 and 22.8 [CH(*C*H$_3$)$_2$], 31.2 (4-C), 47.2 [N*C*H(CH$_3$)Ph and 3-C], 55.8 (OCH$_3$), 60.3 (1-C), 74.3 [*C*H(CH$_3$)$_2$], 110.1 (CH), 120.9 (CH), 126.6 (CH), 127.4 (2 × CH), 128.1 (C), 128.2 (2 × CH), 128.8 (C), 144.9 (C), 146.0 (C), 150.6 (C) ppm. MS: *m*/*z* 339 (M^+, 26%), 324 (75), 192 (29), 150 (53), 105 (100), 43 (52). HRMS: calcd. for $C_{22}H_{29}NO_2$: 339.2198, found: 339.2196.

Bis[(2-benzyl-5-isopropoxy-6-methoxy-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl]mercury (21): During the preparation of THIQ **19a** some off-white solid was observed prior to the reduction step with $NaBH_4$. Some of this material was collected and crystals suitable for structural determination by X-ray crystallography were obtained (m.p. 130–132 °C recrystalised from EtOAc/hexane). IR (film): $\tilde{\nu}_{max}$ = 1727, 1602, 1493, 1439, 1381, 1332, 1279 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, NMR interpretation is for only one unit of the dimeric pair): δ = 1.05 [dd, J = 13.1 and 5.1 Hz, 1 H, C(*H*)-H-Hg], 1.05 [dd, J = 13.1 and 6.1 Hz, 1 H, C(H)*H*-Hg], 1.22–1.25 [m, 6 H, CH(CH_3)$_2$], 2.57 (dd, J = 6.5 and 16.9 Hz, 1 H, 4-H_{eq}), 2.93 (dd, J = 4.6 and 16.9 Hz, 1 H, 4-H_{ax}), 3.42–3.51 [m, 2 H, ArC(*H*)HN and NC(*H*)HPh], 3.63 [d, J = 15.7 Hz, 1 H, NC(H)-*H*Ph], 3.76–3.80 (m under OCH$_3$, 1 H, C*H*CH$_2$Hg), 3.78 (s, 3 H, OCH$_3$), 3.87 [d, J = 13.5 Hz, 1 H, ArC(H)*H*N], 4.39–4.47 [m, 1 H, CH(CH_3)$_2$], 6.58 (d, J = 8.4, 1 H, ArH), 6.66 (d, J = 8.4, 1 H, ArH), 7.21–7.38 (m, 5 H, 5 × ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.7 and 22.8 [CH(*C*H$_3$)$_2$], 33.5 (4-C), 43.5 (CH$_2$-Hg), 51.7 (1-C),[a] 55.9 (OCH$_3$), 57.1 (NCH$_2$Ph),[a] 57.4 (3-C),[a] 74.3 [*C*H(CH$_3$)$_2$], 110.4 (CH), 121.2 (CH), 126.7 (CH), 127.8 (C), 128.2 (2 × CH), 128.7 (2 × CH), 129.7 (C), 139.9 (C), 144.8 (C), 150.8 (C) ppm. MS: *m*/*z* 325 (M^+, 64%), 310 (100), 266 (37), 192 (72), 176 (41). HRMS: calcd. for $C_{21}H_{26}NO_2$ (M^+ – 1) for one THIQ unit: 324.1964, found: 324.1962.

X-ray Crystal Structure of 21: Formula: $C_{42}H_{52}HgN_2O_4$, M = 849.45, colourless needle (crystallized from EtOAc/hexane), crystal size 0.46 × 0.09 × 0.08 mm, a = 28.068(4) Å, b = 7.4349(11) Å, c = 18.689(3) Å, V = 3900(1) $Å^3$, μ = 3.988 mm^{-1}, F(000) = 1720, Z = 4, orthorhombic, space group $Pna2_1$, T = 173(2) K, 23738 reflections collected, 6751 independent reflections, θ_{max} = 26.99°, 449 refined parameters, max./min. residual electron density: 0.988/–1.854 e·$Å^{-3}$. R_1 = 0.0344, wR_2 = 0.0611.

CCDC-637151 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Representative Procedure for Preparing Substituted 5-Isopropoxy-6-methoxy-1,2,3,4-tetrahydrisoquinolines. *n*BuLi-Mediated Cyclization: *n*BuLi (0.16 equiv., 1.4 M) was added to a stirring solution of amine **18** (0.3–0.7 mmol) in THF (10 cm^3). The solution was stirred for 6 h at room temp. after which a further portion of *n*BuLi (0.16 equiv., 1.4 M) was added if required, and the mixture was subsequently heated for another 24 h at 60 °C. The resulting mixture was then extracted with Et_2O (3 × 10 cm^3) which was dried ($MgSO_4$). The organic solvent was removed in vacuo and the crude residue was then purified using column chromatography (5–20% EtOAc/hexane) to afford the substituted 5-isopropoxy-6-methoxy-3-methyl-1,2,3,4-tetrahydroisoquinolines **19**, as light oils. The following THIQs **19** were synthesized according to this procedure. See also the reductive mercuration section for characterization details.

19a: This product was isolated as a yellow oil (0.087 g, 87%), starting from amine **18a** (0.10 g, 0.31 mmol). When the *n*BuLi-mediated cyclization was performed at room temperature on **18a** (0.10 g, 0.31 mmol) an intermediate **22** was observed by TLC. Work-up as described above and purification by a short silica gel plug afforded ***N*-{(3-Isopropoxy-4-methoxy-2-[(1*E*)-prop-1-en-1-yl]phenyl)-methyl}benzylamine (22)** which was identified by NMR spectroscopy. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.20 [d, J = 6.1 Hz, 6 H, CH(CH_3)$_2$], 1.52 (dd, J = 6.8 and 1.6 Hz, 3 H, CHCHCH_3), 1.91 (br. s, 1 H, NH), 3.66 (s, 2 H, ArCH_2N),[a] 3.72 (s, 2 H, NCH_2Ph),[a] 3.82 (s, 3 H, OCH_3), 4.23 [sept, J = 6.1 Hz, 1 H, CH(CH$_3$)$_2$], 5.77–5.88 (m, 1 H, CHCHCH$_3$), 6.34 (br. d, J = 6.1 Hz, 1 H, CHCHCH$_3$), 6.79 (d, J = 8.3 Hz, 1 H, ArH), 7.03 (d, J = 8.3 Hz, 1 H, ArH), 7.20–7.33 (m, 5 H, 5 × ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.2 (CH$_3$), 22.5 [CH(*C*H$_3$)$_2$], 50.8 (ArCH_2N),[b] 53.0 (NCH_2Ph),[b] 55.6 (OCH_3), 75.2 [*C*H(CH$_3$)$_2$], 110.2 (CH), 123.8 (CH), 124.5 (CH), 126.8 (CH), 128.1 (2 × CH), 128.3 (2 × CH), 129.1 (CH), 131.3 (C), 131.6 (C), 140.4 (C), 144.7 (C), 152.1 (C). This compound was then subjected to *n*BuLi (0.16 equiv.) at 60 °C for 18 h and compound **19a** was obtained, after work-up and purification by silica gel column chromatography (10% MeOH/CH_2Cl_2).

19b: This product was isolated as a yellow oil (0.18 g, 90%), starting from amine **18b** (0.20 g, 0.72 mmol).

(±)-19c (3,4-*cis*/*trans* isomers): This product was isolated as a yellow oil (0.126 g, 63%) (5:1 *cis*:*trans*), starting from amine **18c** (0.20 g, 0.59 mmol).

(±)-19d (3,4-*cis*/*trans* isomers): This product was isolated as a yellow oil (0.186 g, 62%), starting from amine **18d** (0.30 g, 1.0 mmol). Determination of the *cis*:*trans* ratio was not posssible due to overlapping peaks in the ^1H spectrum, caused by minor impurities which we were unable to remove by chromatography.

24a: This product was isolated as a yellow oil (0.226 g, 75%) (1:1 diastereoisomeric mixture), starting from amine **23a** (0.30 g, 0.88 mmol). See above for spectroscopy data.

24b: This product was isolated as a yellow oil (0.198 g, 79%) (1:1 diastereoisomeric mixture), starting from amine **23b** (0.25 g, 0.74 mmol). After chromatography, one diastereoisomer was obtained (>95%). This compound's spectroscopic data were identical to the major diasterioisomer reported for **24b**, synthesized using the reductive mercuration procedure as described above.

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