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Stereoselective synthesis of 1,2-diamine containing indolines by a conjugate addition nitro-mannich reaction†

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A conjugate addition nitro-Mannich reaction followed by nitro reduction and intramolecular N-arylation gives diastereomerically pure substituted 1,2-diamine containing indolines. Placing the N-arylation cyclisation handle on the imine precursor derived from an *ortho*-bromine substituted aromatic aldehyde gave the corresponding β-nitroamines in 55–72% yields as single diastereoisomers. Nitro reduction was effected with modified quantities of Zn/HCl and a subsequent Pd(0) catalysed Buchwald Hartwig cyclisation gave indoline products in 40–70% yields as single diastereoisomers.

Introduction

The nitro-Mannich (or aza-Henry) reaction has emerged as a reliable and predictable reaction for the synthesis of β-nitroamines in stereochemically pure form.[1,2] These products have proven useful in the synthesis of many nitrogen containing functional groups including 1,2-diamines,[3–10] α-amino carbonyls,[11–13] peptidomimetics,[14] natural products[15–20] and many heterocyclic small molecules[21–32] of importance to drug discovery. The *anti*-diastereoisomer dominates with higher homologues of nitromethane, with there being only a few methods for *syn*-selective nitro-Mannich reactions.[26,33–35] We reported the enantioselective alkyl conjugate addition nitro-Mannich reaction of dialkyl zincs to nitroalkenes to synthesise complex β-nitroamines containing three contiguous stereocentres (Scheme 1).[36] The judicious choice of solvent determined whether the *syn*,*anti*- or *syn*,*syn*-diastereoisomer was formed and provided another method for the synthesis of *syn*-β-nitroamines. As part of an investigation into using the nitro-Mannich reaction in diversity-oriented array synthesis, we were interested in the synthesis of arrays of stereochemically diverse fused heterocyclic ring systems. We have recently shown that the reductive nitro-Mannich reaction with arylbromide nitrostyrenes can deliver stereodefined functionalised diamine building blocks that are precursors to either 3-aminotetrahydroquinolines or 2-aminomethylene indolines *via* N-arylation (Scheme 1).[37]

We detail here our investigation into the combination of the alkyl conjugate addition nitro-Mannich reaction with suitable aryl bromide containing coupling partners and their subsequent intramolecular cyclisation by palladium catalysed N-arylation to yield novel drug like heterocyclic ring systems (Scheme 2).

Results and discussion

Using conditions previously developed by us, the simplest 2-bromonitrostyrene (**1a**) underwent smooth $Cu(OTf)_2$ catalysed (5 mol%) conjugate addition of $ZnEt_2$ (1.1 equiv.) as judged by TLC. The resultant nitronate species was then reacted with PMP protected imine **2a** (2.2 equiv.) and TFA (2.6 equiv.) with quenching at −78 °C. Crude **3aa** was isolated in a 60 : 40 ratio of two of the possible four diastereoisomers, determined by ^{1}H NMR (Scheme 3). Preliminary investigation of the reaction conditions varied the temperature after TFA addition and the time before quenching. The selectivity tended towards 1 : 1 and the crude product was unstable over time, reverting to starting materials.[38] Usually formation of the corresponding trifluoroacetamide leads to an isolable product, but in this instance the instability of **3aa** and the reluctance of similar *syn*,*syn*-diastereoisomers to be protected, led to the isolation of only 34% of the *syn*,*anti*-**4aa** diastereoisomer as a single diastereoisomer.[36,§] This product was most likely the minor diastereoisomer in the mixture of **3aa**.

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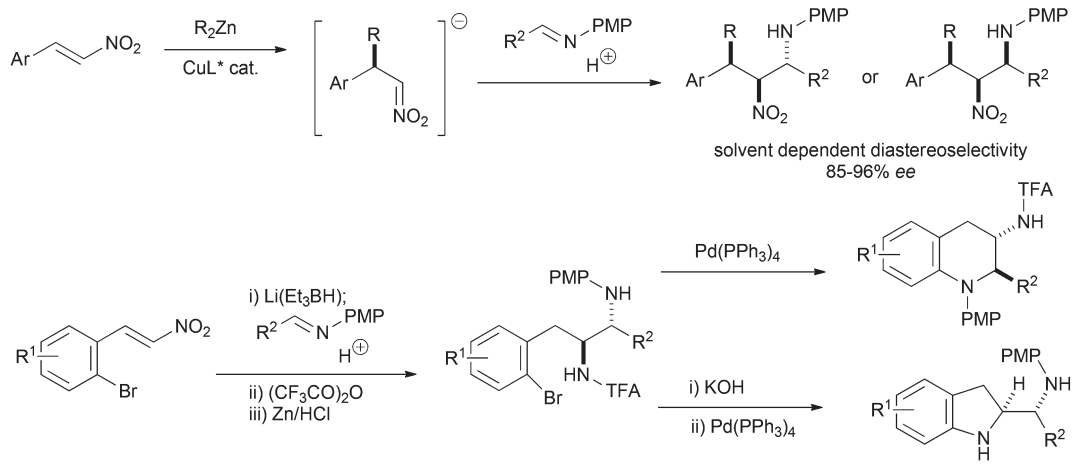
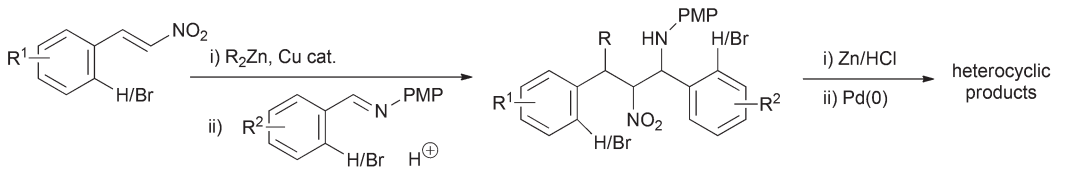
†Electronic supplementary information (ESI) available: General experimental details, X-ray representations and copies of ^{1}H and ^{13}C NMR spectra. CCDC 1020679. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob01793e

‡Corresponding author for crystallographic results.

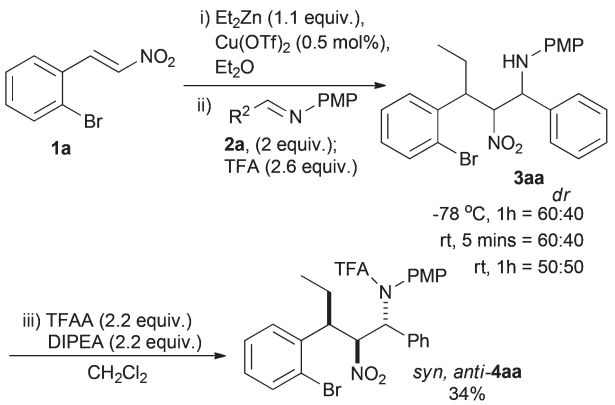
§β-Nitroamines without electron withdrawing protecting groups on nitrogen are known to be unstable to standard purification techniques and undergo retro-addition. See ref. 7 and 36.



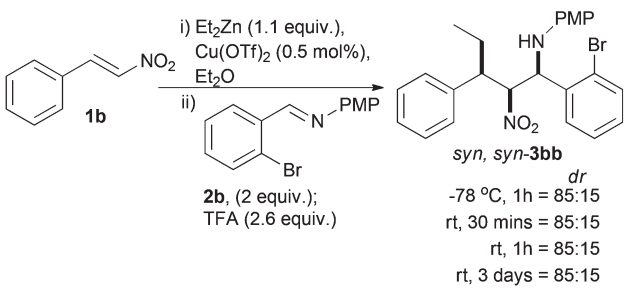
Scheme 1 Previous work.



Scheme 2 Proposed array synthesis of complex heterocycles.



Scheme 3 Preliminary conjugate addition nitro-Mannich reaction.

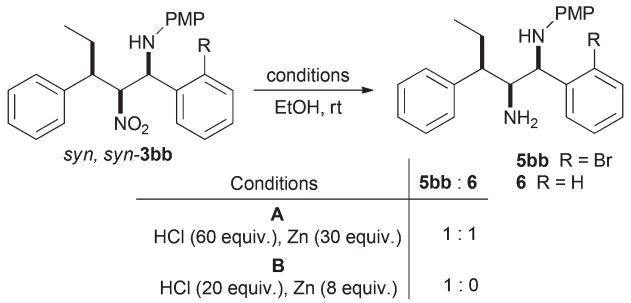


Scheme 4 Stable cyclisation precursor.

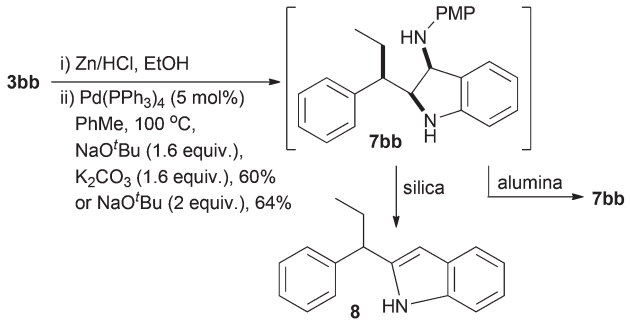
A screen of different protecting groups of the imine partner **2** (COPh, CO_2Bn, $POPh_2$) along with various Lewis and Bronsted acid promoters in place of TFA (AcOH, CF_3SO_3H, $MeSO_3H$, $Yb(OTf)_3$, $AlCl_3$, $Zn(OTf)_2$, $BF_3{\cdot}Et_2O$) was undertaken. Disappointingly no conditions were found that gave either high conversion or a good level of diastereoselectivity with the 2-bromonitrostyrene (**1a**). These results were similar to what we had found in our earlier work with other *ortho*-substituted nitrostyrenes.[36]

An alternative cyclisation precursor was envisaged where the halide coupling partner was part of the aldehyde that the imine was derived from. This small change had a dramatic effect on the extent of diastereoselectivity, and stability of the nitro-Mannich product (Scheme 4). Complete consumption of **1b** was verified by TLC and the reaction went to complete conversion as judged by ^1H NMR. The diastereoselectivity of the crude product did not change over reaction time or temperature after addition of TFA, indicating that the major stereoisomer was thermodynamically stable. We tentatively assigned the stereochemistry as the *syn*,*syn*-diastereoisomer by analogy to previous work where we found that this particular diastereoisomer was relatively stable and could be purified by column chromatography to give diastereomerically pure material.[36] With 2 equivalents of imine **2b** the major diastereoisomer *syn*,*syn*-**3bb** could be isolated in 72% yield¶ and the relative stereochemistry was confirmed by single crystal X-ray analysis (see

¶A minor diastereoisomer was also isolated in 10% yield and is tentatively assigned *anti*,*syn*-**3bb**, by analogy to other work (ref. 36), which has been more rigorously corroborated with single crystal X-ray crystallography. This is based upon the diastereosiomer being stable to purification, so most probably has the *syn*-relative stereochemistry across the nitro-amine bond.



Scheme 5 Nitro reduction.



Scheme 6 Indoline formation.

ESI†). Reducing the quantity of imine **2b** to 1.1 equivalents led to no change in crude diastereoselectivity (85 : 15), but the major compound was significantly easier to purify and was isolated in 68% yield.

A solvent screen (see ESI†) showed that Et_2O gave the highest diastereoselectivity followed by toluene (80 : 20), which contained more side products and unlike Et_2O was a homogenous solution. Other solvents which gave homogeneous reaction mixtures did not give as the major diastereoisomer the *syn*,*anti*-product which had been previously observed with very similar substrates.[36] In most cases the *syn*,*syn*-diastereoisomer was the major compound to varying degrees and all attempts at protection of the amine as a trifluoroacetamide were unsuccessful, which is in agreement with our previous observations for this particular diastereoisomer.[36]

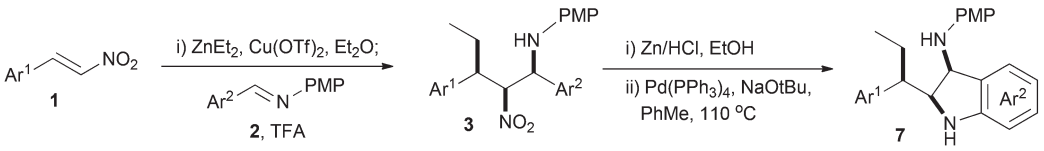
Intramolecular N-arylation required the reduction of the nitro function to an amine. Investigations commenced with **3bb** and initial conditions we have developed for the reduction of β-nitroamines into 1,2-diamines using Zn/HCl (Scheme 5, conditions A).[36–38] Although the nitro group was completely reduced, a 1 : 1 mixture of the desired amine **5bb** and the debrominated material **6** were obtained. Optimisation studies found that reducing the amount of reductant zinc, but increasing the relative amount of HCl lead cleanly to the desired diamine. Normally β-nitroamines (like **3bb**) would be isolated as their corresponding trifluoroacetamides and subsequent reduction is accompanied by migration of the trifluoroacetyl group to the primary nitrogen, giving a stable isolable product.[36–38] However, as the *syn*,*syn*-diastereoisomers like **3bb** are in general inert to trifluoroacetylation,[36] the resultant 1,2-diamine reduction product **5bb** was found to become less pure upon column chromatography. As a consequence intramolecular cyclisation using palladium catalysed N-arylation was attempted on the crude reduction material.

Treatment of **5bb** under standard $Pd(PPh_3)_4$ Buchwald–Hartwig conditions that we have used to perform analogous cyclisations (Scheme 1),[37] led cleanly to the indoline **7bb** by ^1H NMR of the crude cyclisation product (Scheme 6). Initial attempts at purification using silica gel chromatography led to degradation and isolation of the corresponding indole **8** (~25%) as a mixture with *p*-anisidine. Indoline **7bb** is unstable to acidic conditions, but using basic alumina chromatography we were able to isolate **7bb** in a good 60% yield over two steps as a single diastereoisomer. Use solely of NaO^tBu as base led to 64% yield of indoline **7bb** (Scheme 6).

The scope of this reaction sequence for the synthesis of the 1,2-diamine indolines was then investigated with a series of aldimines containing an *ortho*-bromine susbstituent and nitro styrenes under the optimised conditions described above (Scheme 7 and Table 1).

The conjugate addition nitro-Mannich reaction proceeds well with a range of imines **1** and nitrostyrenes **2** to give good diastereoslectivites of *syn*,*syn*-products and good isolated yields of diastereomerically pure β-nitroamines **3**. The reductions proceeded smoothly except for the β-nitroamine derived from 2-bromo-3-pyridinylaldehyde (entry 6), which led to an inseparable mixture of unidentified products. Use of Sn/HCl gave similar results and Al/Hg amalgam, which we have used for the reduction of sensitive β-nitroamines,[39] gave a complex mixture of products. No doubt the sensitivity of the pyridine function and the C–Br bond are both compounding this reduction. Cyclisations to give the indoline nucleus by standard $Pd(PPh_3)_4$ Buchwald–Hartwig conditions gave good yields in most cases. The β-nitroamine derived from 2-bromo-5-methoxy benzaldehyde (entry 3) cyclised using $Pd(PPh_3)_4$ albeit with a moderate yield of 40%. The congener derived from 2-bromo-4,5-dimethoxy benzaldehyde (entry 4) failed to cyclise and gradually led to decomposition of the β-nitroamine over longer reaction times. Changing to a Binap or X-Phos ligand system, which is known to coupling electron rich aryl bromides,[40] also led to gradual decomposition.

With respect to the conjugate addition of other carbon nucleophiles, we have already shown that methyl and phenyl dialkylzinc species work in the conjugate addition nitro-Mannich reaction and led to *syn*,*syn*-β-nitroamines in high diastereoselectivity.[36] There are a number of chiral metal catalysed systems that control the enantioselectivity of dialkyl zinc addition to nitro-alkenes and we have already shown that this is a good way of making the conjugate addition nitro-Mannich products enantioselectively,[36] which would in turn lead to the heterocyclic products described here in enantiomerically pure form. This methodology is limited by the availability of dialkylzincs and although it is possible to add functionalised dialkyl zincs that can be derived from the tandem hydroboration/boron-zinc exchange method developed by Knochel,[41] it would

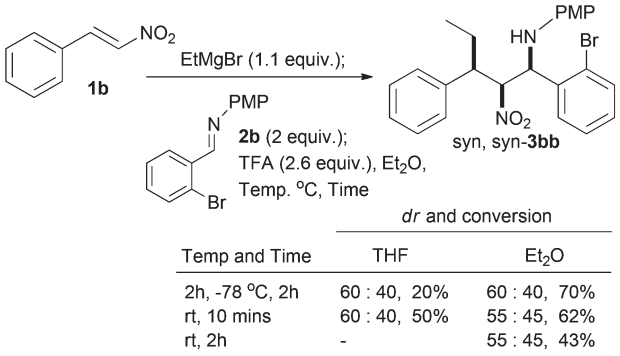


Scheme 7 Scope of indoline formation.

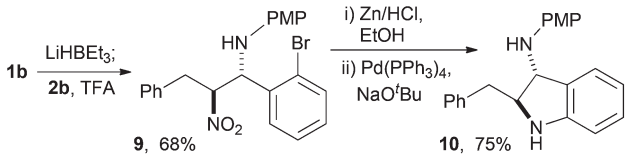
Table 1 Scope of indoline formation[a]

Entry	Ar^1	Ar^2	3 dr crude[b]	Yield 3[c] (%)	Yield 7[c] (%)
1	Ph	2-BrPh	85 : 15	68	64
2	Ph	2-Br-5-FPh	90 : 10	72	53
3	Ph	2-Br-5-MeOPh	80 : 20	63	40
4	Ph	2-Br-4,5-$(MeO)_2$Ph	80 : 20	57	0[d]
5	Ph	2-Br-4-MePh	85 : 15	63	64
6	Ph	2-Br-3-pyridinyl	80 : 20	55	0[e]
7	4-MePh	2-BrPh	80 : 20	64	64
8	2-MePh	2-BrPh	80 : 20	62	66
9	4-FPh	2-BrPh	75 : 25	62	70

[a] Nitro-Mannich: **1** (3 mmol), $Cu(OTf)_2$ (5 mol%), $ZnEt_2$ (1.1 equiv.), Et_2O, −78 °C, 5 min, then RT 2 h; **2** (1.1 equiv.), Et_2O, −78 C, 10 min; TFA (2.6 equiv.), Et_2O, −78 °C, 1 h then to RT 1 h. Nitro reduction: conc. HCl (10 mmol) added to **3** (0.50 mmol), Zinc (4.00 mmol), in EtOH (7.5 mL) at 0 °C, 5 min then RT. N-arylation: crude 1,2-diamine in PhMe (1.5 ml) added to NaO^{t}Bu (1.00 mmol), $Pd(PPh_3)_4$ (0.025 mmol) in PhMe (1 ml) at RT then 90 °C, 16–24 h. [b] Diastereoselectivities were calculated by comparison of the ^{1}H NMR signals for the C*H*CHNO$_2$ protons (δ 3.1–3.6 ppm) of the crude reaction mixture. [c] Isolated yield of pure *syn*,*syn*-diastereoisomer. [d] Reaction failed at cyclisation. [e] Reaction failed at reduction.



Scheme 8 Use of Grignard nucleophile.



Scheme 9 Sequence using the reductive nitro-Mannich reaction.

be better if more readily available carbon nucleophiles could be found. In an attempt to widen the scope of the reaction to include organozinc halides‖,[42,43] test reactions revealed that benzylzinc bromide and allylzinc bromide both gave low diastereoselectivities and trace conversions (<10%) with **1b** and **2b** in THF and Et_2O. By TLC the reactions seem to falter at the conjugate addition stage. Exploration of Grignard reagents was not successful with vinyl magnesium bromide, but changing to ethylmagnesium bromide gave an optimised yield of 70% (Scheme 8), but unfortunately a significant drop in diastereoselectivity (60 : 40).

We have found nucleophilic hydride useful in the conjugate addition nitro-Mannich reaction[38,44] and with these particular substrates use of super hydride® led to *anti*-β-nitroamine **9**, that could be smoothly reduced and cyclised to give the indoline **10** in 75% yield from **9** (Scheme 9). The sense of diastereoselection was *anti*- as previously described for other *ortho*-substituted aldimines.[38]

Conclusion

We have developed a diastereoselective synthesis of substituted 1,2-diamine containing indolines, that represent novel drug like heterocyclic ring systems, from a conjugate addition nitro-Mannich reaction followed by nitro reduction and intramolecular N-arylation. Attempts to make indoline precursors from nitro styrenes containing an *ortho*-bromine substituent were low yielding and poorly diastereoselective (Scheme 3). Placing the N-arylation cyclisation handle on the imine precursor derived from an *ortho*-bromine substituted aromatic aldehyde was much more successful giving the corresponding β-nitroamine in good yield and as a single diastereoisomer. Nitro reduction was effected with modified quantities of Zn/HCl and a subsequent Pd(0) catalysed Buchwald Hartwig cyclisation gave indoline products in good yields as single diastereoisomers (Table 1). Electron rich aryl bromides were found to be reluctant to cyclise. Despite exploring other more readily available organometallic carbon nucleophiles, especially organozinc halides, a limitation to the current methodology is that dialkyl zinc species are the most efficient for the initial conjugate addition to nitro styrene. We have previously modified literature protocols to enable the enantioselective synthesis of suitably functionalised β-nitroamines for cyclisation to functionalised heterocycles[36,37,44] and this methodology could also be used in this case. We are investigating the use of other nucleophiles to trigger this reaction and alternative cyclisation modes are being investigated to prepare alternate ring systems and will be reported in due course.

‖ Alkyl/aryl zinc halides have been shown to be useful in certain addition and conjugate addition reactions.

Experimental section

General procedure for the synthesis of *syn*,*syn*-β-nitroamines 3 (Table 1)

To a stirred mixture of nitroalkene (3.00 mmol) and $Cu(OTf)_2$ (0.05 mmol) in Et_2O (5 mL) at −78 °C was added Et_2Zn (3.3 mmol, 1 M in hexanes) dropwise. The mixture was stirred at this temperature for 5 min then at RT until the reaction was complete by TLC analysis (approximately 2 h). The reaction mixture was cooled to −78 °C and a solution of imine (3.3 mmol) in dry Et_2O (5 mL) was added and the mixture stirred for 10 min. Then a solution of TFA (7.8 mmol) in Et_2O (0.2 mL) was added dropwise over 20 s and the reaction stirred for 1 h. The reaction was warmed to room temperature over 1 h to provide a suspension of white solid in a vivid yellow supernatant. The reaction was quenched by the addition of Et_2O and saturated aq. $NaHCO_3$. The layers were separated, and the aqueous phase was extracted with Et_2O. The organic layers were combined, and the solvent was removed *in vacuo* to provide crude β-nitroamine. Diastereoselectivities were calculated by comparison of the ^{1}H NMR signals for the C*H*CHNO$_2$ protons (δ 3.1–3.6 ppm). Purification by flash chromatography yielded diastereomerically pure *syn*,*syn*-β-nitroamines **3**.

***syn*,*anti*-4aa (1*R**,2*S**,3*R**)-*N*-(1-(2-Bromophenyl)-2-nitro-3-phenylpentyl)-*N*-trifluoroacetyl-4-methoxybenzenamine.** Prepared according to our previously published work on a 3 mmol scale.[38] Pale yellow oil (34%) ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.87 (3H, t, *J* = 7.3), 1.82 (1H, ddq, *J* = 13.7, 10.5, 7.3), 2.04 (1H, dqd, *J* = 13.7, 7.3, 4.6), 3.77 (3H, s), 4.13 (1H, ddd, *J* = 10.5, 6.2, 4.5), 5.78 (1H, br. s), 5.90 (1H, m), 5.92 (1H, dd, *J* = 8.8, 2.7), 6.55 (1H, dd, *J* = 8.8, 2.9), 6.71 (1H, br. d, *J* = 8.3), 6.76 (1H, dd, *J* = 8.8, 2.9), 7.10 (2H, d, *J* = 7.4), 7.21 (1H, ddd, *J* = 8.1, 7.2, 1.8), 7.22 (2H, m), 7.29 (1H, tt, *J* = 7.2, 1.2), 7.34 (1H, ddd, *J* = 7.8, 7.2, 1.3), 7.38 (1H, dd, *J* = 7.9, 1.8), 7.67 (1H, dd, *J* = 8.1, 1.4); ^{13}C NMR (126 MHz, $CDCl_3$): δ 11.5 (*C*H$_3$), 26.5 (*C*H$_2$), 45.9 (*C*H), 55.6 (*C*H$_3$), 63.6 (*C*H), 90.0 (*C*H), 113.6 (*C*H), 114.1 (*C*H), 116.2 (*C*H, d, *J* = 288.4), 127.2 (q), 128.1 (q), 128.3 (*C*H), 128.6 (*C*H), 128.7 (*C*H), 128.8 (2x*C*H), 129.4 (*C*H), 129.5 (2x*C*H), 130.7 (*C*H), 131.9 (*C*H), 133.6 (*C*H), 134.3 (q), 137.7 (q), 158.4 (*C*H, d, *J* = 35.5), 160.2 (q); IR ν_{max} (neat) 2968, 2935, 1695, 1553, 1510, 1254 cm^{-1}; HRMS (EI) calcd for $C_{26}H_{24}BrF_3N_2O_4^+$, [M$^+$] 564.0866 found 564.0856.

***syn*,*syn*-3bb Entry 1(1*S**,2*S**,3*R**)-*N*-(1-(2-Bromophenyl)-2-nitro-3-phenylpentyl)-4-methoxybenzenamine.** Yellow solid (68%) m.p. 117–118 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.77 (3H, t, *J* = 7.3), 1.63 (1H, dqd, *J* = 13.5, 7.3, 3.6), 1.61 (1H, ddq, *J* = 13.5, 11.7, 7.3), 3.65 (1H, app. td, *J* = 11.5, 3.5), 3.66 (3H, s), 4.56 (1H, dd, *J* = 10.4, 3.2), 5.05 (1H, dd, *J* = 11.3, 3.4), 6.20 (2H, m), 6.62 (2H, m), 7.07 (2H, m), 7.16 (1H, m), 7.26 (1H, m), 7.45 (1H, d, *J* = 7.8); ^{13}C NMR (126 MHz, $CDCl_3$): δ 11.4 (*C*H$_3$), 24.8 (*C*H$_2$), 47.8 (*C*H), 55.2 (*C*H$_3$), 55.7 (*C*H), 95.2 (*C*H), 114.0 (2C, *C*H), 114.5 (2C, *C*H), 122.8 (*C*H), 122.8 (q), 127.1 (*C*H), 127.5 (*C*H), 127.9 (*C*H), 128.4 (2C, *C*H), 128.6 (2C, *C*H), 129.4 (*C*H), 132.8 (*C*H), 136.5 (q), 136.8 (q), 139.1 (q), 152.0 (q); IR ν_{max} (neat) 3408, 2967, 1550, 1243 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{25}BrN_2O_3^+$, [M$^+$] 468.1043 found 468.1035. *Minor diastereoisomer*. Pale yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.73 (3H, t, *J* = 7.3), 1.74–1.85 (1H, m), 1.97–2.09 (1H, m), 3.61 (1H, app. td, *J* = 11.1, 3.8), 3.71 (3H, s), 5.23 (1H, dd, *J* = 11.1, 3.6), 5.31 (1H, d, *J* = 9.8), 5.47 (1H, dd, *J* = 9.8, 3.6), 6.49–6.56 (2H, m), 6.70–6.80 (2H, m), 7.09–7.25 (6H, m), 7.28–7.33 (2H, m), 7.55–7.61 (1H, m); ^{13}C NMR (151 MHz, $CDCl_3$): δ 11.8 (*C*H$_3$), 24.1 (*C*H$_2$), 48.4 (*C*H), 55.6 (O*C*H$_3$), 55.8 (*C*H), 95.7 (*C*H), 114.0 (2C, *C*H), 115.1 (2C, *C*H), 123.3 (q), 127.7 (*C*H), 127.8 (*C*H), 128.2 (2C, *C*H), 128.6 (*C*H), 128.9 (2C, *C*H), 130.0 (*C*H), 133.3 (*C*H), 136.5 (q), 138.5 (q), 139.5 (q), 152.6 (q); IR ν_{max} (neat) 3403, 2967, 1552, 1243 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{25}BrN_2O_3^+$, [M$^+$] 468.1043 found 468.1035.

Entry 2 (1*S,2*S**,3*R**)-*N*-(1-(2-Bromo-5-fluorophenyl)-2-nitro-3-phenylpentyl)-4-methoxybenzenamine.** Yellow solid (72%) m.p. 123–124 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.76 (3H, t, *J* = 7.3), 1.63 (1H, dqd, *J* = 13.4, 7.3, 3.5), 1.80 (1H, dqd, *J* = 13.4, 11.6, 7.3), 3.64 (1H, td, *J* = 11.4, 3.5), 3.67 (3H, s), 4.50 (1H, dd, *J* = 10.2, 3.3), 5.05 (1H, dd, *J* = 11.4, 3.3), 5.22 (1H, d, *J* = 10.2), 6.19–6.22 (2H, m), 6.62–6.65 (2H, m), 6.80 (1H, ddd, *J* = 8.6, 7.6, 3.0), 7.16 (1H, dd, *J* = 9.2, 3.0), 7.24–7.30 (5H, m), 7.43 (1H, dd, *J* = 8.6, 5.0); ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.2 (*C*H$_3$), 25.1 (*C*H$_2$), 48.3 (*C*H), 55.7 (*C*H$_3$), 56.2 (*C*H), 95.2 (*C*H), 114.3 (2C, *C*H), 114.9 (2C, *C*H), 115.0 (d, J_{CF} = 24.2, *C*H), 116.9 (d, J_{CF} = 2.7, q), 117.2 (d, J_{CF} = 22.9, *C*H), 128.0 (*C*H), 128.9 (2C, *C*H), 129.0 (2C, *C*H), 134.5 (d, J_{CF} = 7.7, *C*H), 137.0 (q), 139.0 (q), 139.6 (d, J_{CF} = 5.9, q), 152.5 (q), 162.5 (d, J_{CF} = 249.0, q); IR ν_{max} (neat) 3417, 2966, 1550, 1242, cm^{-1}; HRMS (EI) calcd for $C_{24}H_{24}BrFN_2O_3^+$, [M$^+$] 486.0948 found 486.0934; Anal. calcd for $C_{24}H_{24}BrFN_2O_3$: C, 59.15; H, 4.96; N, 5.75; found: C, 59.09; H, 4.89; N, 5.78%.

Entry 3 (1*S,2*S**,3*R**)-*N*-(1-(2-bromo-5-methoxyphenyl)-2-nitro-3-phenylpentyl)-4-methoxyaniline.** Yellow solid (63%) m.p. 148–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.75 (3H, t, *J* = 7.3), 1.63 (1H, dqd, *J* = 13.5, 7.3, 3.5), 1.80 (1H, ddq, *J* = 13.5, 11.3, 7.3), 3.56–3.66 (1H, m), 3.64 (3H, s), 3.666 (3H, s), 4.64 (1H, m), 5.06 (1H, dd, *J* = 11.3, 3.5), 5.20 (1H, br. s), 6.15–6.28 (2H, m), 6.56–6.69 (4H, m), 7.21–7.39 (6H, m); ^{13}C NMR (101 MHz, $CDCl_3$): δ 11.6 (*C*H$_3$), 25.2 (*C*H$_2$), 48.2 (*C*H), 55.3 (*C*H$_3$), 55.6 (*C*H$_3$), 56.2 (*C*H), 95.5 (*C*H), 113.1 (q), 113.6 (*C*H) 114.3 (2C, *C*H), 114.8 (2C, *C*H), 115.2 (*C*H), 127.8 (*C*H), 128.7 (2C, *C*H), 128.9 (2C, *C*H), 133.7 (*C*H), 137.1 (q), 138.0 (q), 139.5 (q), 152.3 (q), 159.5 (q); IR ν_{max} (neat) 3406, 2935, 1550, 1240 cm^{-1}; HRMS (ES) calcd for $C_{25}H_{28}BrN_2O_4^+$, [M + H$^+$] 499.1232 found 499.1236.

Entry 4 (1*S,2*S**,3*R**)-*N*-(1-(2-bromo-4,5-dimethoxyphenyl)-2-nitro-3-phenylpentyl)-4-methoxybenzenamine.** Yellow solid (57%) m.p. 53–55 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.75 (3H, t, *J* = 7.3), 1.62 (1H, dqd, *J* = 13.5, 7.3, 3.5), 1.79 (1H, ddq, *J* = 13.5, 11.7, 7.3), 3.60 (1H, td, *J* = 11.4, 3.5), 3.67 (3H, s), 3.69 (3H, s), 3.80 (3H, s), 4.45 (1H, dd, *J* = 10.0, 3.4), 5.00 (1H, dd, *J* = 11.4, 3.4), 5.19 (1H, d, *J* = 10.0), 6.20–6.23 (2H, m), 6.55 (1H, s), 6.60–6.63 (2H, m), 6.90 (1H, s), 7.24–7.29 (5H, m); ^{13}C NMR (126 MHz, $CDCl_3$): δ 11.7 (*C*H$_3$), 25.2 (*C*H$_2$), 48.3 (*C*H), 55.7 (*C*H$_3$), 56.1 (*C*H$_3$), 56.1 (*C*H), 56.2 (*C*H$_3$), 95.9 (*C*H), 109.8 (*C*H), 114.4 (2C, *C*H), 114.9 (2C, *C*H), 115.6 (*C*H), 127.9 (*C*H), 128.8 (2C, *C*H), 128.9 (2C, *C*H), 134.5 (*C*H), 137.2 (q), 139.6 (q), 149.0

(q), 149.3 (q), 152.3 (q); IR ν_{max} (neat) 3399, 2965, 1549, 1258 cm^{-1}; HRMS (EI) calcd for $C_{26}H_{29}BrN_2O_5^+$, [M^+] 528.1254 found 528.1254.

Entry 5 (1*S,2*S**,3*R**)-*N*-(1-(2-bromo-4-methylphenyl)-2-nitro-3-phenylpentyl)-4-methoxyaniline.** Yellow solid (63%) m.p. 97–99 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.75 (3H, t, J = 7.3), 1.63 (1H, dqd, J = 13.6, 7.3, 3.6), 1.78 (1H, ddq, J = 13.6, 11.3, 7.3), 2.21 (3H, s), 3.57–3.70 (1H, m), 3.65 (3H, s), 4.48–4.57 (1H, m, J = 10.3, 3.3), 5.04 (1H, dd, J = 11.3, 3.5), 5.18 (1H, d, J = 9.3), 6.14–6.27 (2H, m), 6.53–6.67 (2H, m), 6.89–7.00 (2H, m), 7.19–7.32 (6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 11.6 (*C*H_3), 20.6 (*C*H_3), 25.2 (*C*H_2), 48.2 (*C*H), 55.6 (*C*H_3), 55.8 (*C*H), 95.7 (*C*H), 114.4 (2C, *C*H), 114.8 (2C, *C*H, 122.8 (q), 127.0 (*C*H), 127.8 (*C*H), 128.7 (2C, *C*H), 128.9 (2C, *C*H), 128.9 (*C*H), 133.6 (*C*H), 133.7 (q), 137.2 (q), 139.5 (q), 139.9 (q), 152.3 (q); IR ν_{max} (neat) 3415, 2932, 1550, 1243 cm^{-1}; HRMS (EI) calcd for $C_{25}H_{28}BrN_2O_3^+$, [M + H^+] 483.1278 found 483.1283.

Entry 6 (1*S,2*S**,3*R**)-*N*-(1-(2-bromopyridin-3-yl)-2-nitro-3-phenylpentyl)-4-methoxyaniline.** Yellow solid (55%) m.p. 143–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.75 (3H, t, J = 7.3), 1.63 (1H, dqd, J = 13.5, 7.3, 3.5), 1.81 (1H, ddq, J = 13.5, 11.3, 7.3), 3.53–3.70 (1H, m), 3.65 (3H, s), 4.44–4.56 (1H, m), 5.09 (1H, dd, J = 11.3, 3.3), 5.18 (1H, d, J = 9.5), 6.11–6.25 (2H, m), 6.56–6.66 (2H, m), 7.11 (1H, dd, J = 7.7, 4.6), 7.20–7.34 (5H, m), 7.40 (1H, dd, J = 7.7, 1.9), 8.20 (1H, dd, J = 4.6, 1.9); ^{13}C NMR (101 MHz, $CDCl_3$): δ 11.6 (*C*H_3), 25.2 (*C*H_2), 48.1 (*C*H), 55.6 (*C*H_3), 55.7 (*C*H_3), 95.1 (*C*H), 114.3 (2C, *C*H), 115.0 (2C, *C*H), 123.5 (*C*H), 128.0 (*C*H), 128.7 (2C, *C*H), 128.8 (2C, *C*H), 134.7 (q), 136.1 (*C*H), 136.8 (q), 138.8 (q), 142.8 (q), 149.7 (*C*H), 152.6 (q); IR ν_{max} (neat) 3414, 2934, 1548, 1241 cm^{-1}; HRMS (ES) calcd for $C_{23}H_{25}BrN_3O_3^+$, [M + H^+] 469.1079 found 469.1080.

Entry 7 (1*S,2*S**,3*R**)-*N*-(1-(2-bromophenyl)-2-nitro-3-*p*-tolylpentyl)-4-methoxybenzenamine.** Yellow solid m.p. 143–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.77 (3H, t, J = 7.3), 1.63 (1H, dqd, J = 13.6, 7.3, 3.6), 1.79 (1H, ddq, J = 13.6, 11.7, 7.3), 2.35 (3H, s), 3.63 (1H, app. td, J = 11.3, 3.5), 3.68 (3H, s), 4.64 (1H, dd, J = 10.3, 3.3), 5.07 (1H, dd, J = 11.2, 3.3), 5.25 (1H, d, J = 10.3), 6.19–6.29 (2H, m), 6.59–6.69 (2H, m), 7.04–7.21 (7H, m), 7.49 (1H, dd, J = 7.8, 1.0); ^{13}C NMR (101 MHz, $CDCl_3$): δ 11.6 (*C*H_3), 21.1 (*C*H_3), 25.2 (*C*H_2), 47.7 (*C*H), 55.6 (O*C*H_3), 56.0 (*C*H), 95.6 (*C*H), 114.3 (2C, *C*H), 114.8 (2C, *C*H), 123.1 (q), 127.4 (*C*H), 128.1 (*C*H), 128.7 (2C, *C*H), 129.4 (2C, *C*H), 129.6 (*C*H), 133.1 (*C*H), 134.0 (q), 137.0 (q), 137.4 (q), 139.5 (q), 152.3 (q); IR ν_{max} (neat) 3415, 2933, 1550, 1243 cm^{-1}; HRMS (ES) calcd for $C_{25}H_{28}BrN_2O_3^+$, [M + H^+] 483.1278 found 483.2181.

Entry 8 (1*S,2*S**,3*R**)-*N*-(1-(2-bromophenyl)-2-nitro-3-*o*-tolylpentyl)-4-methoxybenzenamine.** Yellow solid (62%) m. p. 119–121 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.72 (3H, t, J = 7.3), 1.77 (1H, ddq, J = 12.7, 11.2, 7.3), 2.07 (1H, dqd, J = 12.7, 7.3, 4.0), 2.39 (3H, s), 3.71 (3H, s), 4.10 (1H, app. td, J = 11.1, 3.9), 5.28 (1H, dd, J = 11.1, 3.3), 5.30 (1H, d, J = 10.2), 5.50 (1H, dd, J = 10.2, 3.3), 6.54–6.58 (2H, m), 6.74–6.78 (2H, m), 7.10–7.15 (5H, m), 7.17–7.22 (2H, m), 7.23–7.27 (1H, m), 7.60 (1H, d, J = 8.0); ^{13}C NMR (126 MHz, $CDCl_3$): δ 11.2 (*C*H_3), 19.9 (*C*H_3) 25.2 (*C*H_2), 42.0 (*C*H), 55.7 (*C*H_3), 55.8 (*C*H), 95.5 (*C*H), 114.5 (2C, *C*H), 115.1 (2C, *C*H), 123.3 (q), 125.8 (*C*H), 126.6 (*C*H), 127.2 (*C*H), 127.5 (*C*H), 128.6 (*C*H), 130.0 (*C*H), 130.8 (*C*H), 133.3 (*C*H), 136.6 (q), 137.1 (q), 137.4 (q), 139.5 (q), 152.6 (q); IR ν_{max} (neat) 3399, 2965, 1549, 1258 cm^{-1}; HRMS (EI) calcd for $C_{25}H_{27}BrN_2O_3^+$, [M^+] 482.1199 found 482.1185; Anal. calcd for $C_{25}H_{27}BrN_2O_3$: C, 62.12; H, 5.63; N, 5.80; found: C, 62.09; H, 5.90; N, 5.63%.

Entry 9 (1*S,2*S**,3*R**)-*N*-(1-(2-bromophenyl)-3-(4-fluorophenyl)-2-nitropentyl)-4-methoxybenzenamine.** Yellow solid (62%) m.p. 117–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.76 (3H, t, J = 7.3), 1.65 (1H, dqd, J = 13.4, 7.3, 3.5), 1.77 (1H, dqd, J = 13.4, 11.4, 7.3), 3.67 (1H, m), 3.68 (3H, s), 4.57 (1H, app. d, J = 6.5), 5.03 (1H, dd, J = 11.2, 3.4), 5.23 (1H, d, J = 9.3), 6.20–6.28 (2H, m), 6.60–6.70 (2H, m), 6.96–7.04 (2H, m), 7.05–7.14 (2H, m), 7.14.7.22 (1H, m), 7.22–7.32 (2H, m), 7.49 (1H, d, J = 8.1); ^{13}C NMR (101 MHz, $CDCl_3$): δ 11.6 (*C*H_3), 25.2 (*C*H_2), 47.4 (*C*H), 55.6 (*C*H_3), 56.0 (*C*H), 95.4 (*C*H), 114.3 (2C, *C*H), 114.9 (2C, *C*H), 115.7 (d, J_{CF} = 21.6, 2C, *C*H), 123.1 (q), 127.4 (*C*H), 128.2 (*C*H), 129.8 (*C*H), 130.4 (d, J_{CF} = 7.2, 2C *C*H), 132.9 (d, J_{CF} = 3.2, q), 133.2 (q), 136.6 (q), 139.3 (q), 152.4 (q), 162.3 (d, J_{CF} = 246.7, q); ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.70 (m); IR ν_{max} (neat) 3413, 2967, 1550, 1228 cm^{-1}; HRMS (ES) calcd for $C_{24}H_{25}BrFN_2O_3^+$, [M + H^+] 487.1027 found 487.1026.

General procedure for the synthesis of indolines 7 (Table 1)

To a stirred mixture of *syn*,*syn*-β-nitroamine **3** (0.50 mmol) and Zinc (4.00 mmol) in EtOH (7.5 mL) at 0 °C was added conc. hydrochloric acid (10 mmol). The mixture was stirred at this temperature for 5 min then at RT until the reaction was complete by TLC analysis (approximately 1 h). The reaction was quenched by the addition of EtOAc and saturated aq. $NaHCO_3$. The layers were separated, and the aqueous phase was extracted with EtOAc. The organic layers were combined, and the solvent was removed *in vacuo* to provide crude 1,2-diamine.

To a stirred mixture of sodium *tert*-butoxide (1.00 mmol), palladium tetrakistriphenylphosphine (0.025 mmol) in toluene (1 ml) under nitrogen at RT was added a solution of crude 1,2-diamine in toluene (1.5 ml). The reaction vessel was heated at 90 °C until the reaction was complete by TLC analysis (approximately 16 to 24 h). Reaction cooled to RT and filtered thought celite and concentrated to give a brown oil. Purification by flash chromatography using basic Alumina or aminopropyl (NH_2) silica yielded the indoline 7 (Table 1).

7bb Entry 1 (1*S,2*S**,1′*R**)-1-*N*-(4-methoxyphenyl)-2-(1′-phenylpropyl)indolin-3-amine.** Yellow oil (64%); ^{1}H NMR (600 MHz, C_6D_6): δ 0.75 (3H, t, J = 7.3), 1.77 (1H, ddq, J = 13.1, 11.5, 7.3), 1.65 (1H, dqd, J = 13.1, 7.3, 3.6), 3.10 (1H, ddd, J = 11.3, 10.4, 3.6), 3.16 (1H, d, J = 10.7), 3.31 (3H, s), 3.51 (1H, ddd, J = 10.4, 6.6, 3.0), 3.62 (1H, d, J = 3.0), 4.14 (1H, dd, J = 10.7, 6.6), 5.94–5.97 (2H, m), 6.58 (1H, d, J = 7.8), 6.60–6.65 (3H, m), 6.91 (1H, d, J = 7.2), 7.07–7.12 (2H, m), 7.13–7.17 (4H, m); ^{13}C NMR (151 MHz, C_6D_6): δ 10.7 (*C*H_3), 24.9 (*C*H_2), 45.7 (*C*H), 53.8 (*C*H_3), 57.9 (*C*H), 67.5 (*C*H), 109.1 (*C*H), 113.5 (2C, *C*H), 115.4 (2C, *C*H), 118.0 (*C*H), 123.1 (*C*H), 125.1 (*C*H), 127.1 (2C, *C*H), 127.5 (*C*H), 127.7 (2C, *C*H), 131.1 (*q*), 140.5 (q), 141.6 (q), 149.2 (q), 151.8 (q); IR ν_{max} (neat) 3367, 2928, 1234 cm^{-1};

HRMS (EI) calcd for $C_{24}H_{26}N_2O^+$, [M^+] 358.2040 found 358.2028.

Entry 2 (1*S,2*S**,1′*R**)-5-fluoro-*N*-(4-methoxyphenyl)-2-(1′-phenylpropyl)indolin-3-amine.** Yellow oil (53%); ^{1}H NMR (600 MHz, C_6D_6): δ 0.76 (3H, t, J = 7.3), 1.39 (1H, ddq, J = 13.2, 11.4, 7.3), 1.61 (1H, dqd, J = 13.2, 7.3, 3.6), 3.03–3.07 (2H, m), 3.30 (3H, s), 3.51 (2H, m), 3.98 (1H, dd, J = 10.2, 6.6), 5.89–5.92 (2H, m), 6.58 (1H, dd, J = 8.5, 4.2), 6.58–6.61 (2H, m), 6.66 (1H, dd, J = 8.0, 2.6), 6.78 (1H, dd, J = 8.7, 2.6), 7.09–7.17 (5H, m); ^{13}C NMR (151 MHz, C_6D_6): δ 11.9 (*C*H$_3$), 26.2 (*C*H$_2$), 46.9 (*C*H), 54.9 (*C*H$_3$), 59.2 (*C*H), 69.3 (*C*H), 115.0 (d, J_{CF} = 31.2, *C*H), 116.9 (d, J_{CF} = 23.2, *C*H), 114.8 (2C, *C*H), 114.9 (d, J_{CF} = 23.2, *C*H), 116.8 (2C, *C*H), 126.5 (*C*H), 128.2 (*C*H), 128.4 (2C, *C*H), 128.9 (*C*H), 133.7 (d, J_{CF} = 7.3, q), 141.2 (q), 142.6 (q), 146.4 (q), 153.3 (q), 157.1 (d, J_{CF} = 236.0, q); IR ν_{max} (neat) 3365, 2961, 1509, 1236 cm^{-1}; HRMS (CI) calcd for $C_{24}H_{26}FN_2O^+$, [M + H$^+$] 377.2029 found 377.2028.

Entry 3 (1*S,2*S**,1′*R**)-5-methoxy-*N*-(4-methoxyphenyl)-2-(1′-phenylpropyl)indolin-3-amine.** Light yellow oil (40%); ^{1}H NMR (400 MHz, CDCN): δ 0.72 (3H, t, J = 7.4), 1.66 (1H, ddq, J = 13.1, 11.5, 7.3), 1.86–1.94 (1H, m), 3.02 (1H, app. td, J = 10.4, 3.5), 3.58 (3H, s), 3.66 (3H, s), 3.88–4.03 (2H, m), 4.28 (1H, dd, J = 9.5, 7.0), 4.55 (1H, br. s), 6.25–6.36 (2H, m), 6.52 (1H, s), 6.60–6.69 (4H, m), 7.13–7.27 (5H, m); ^{13}C NMR (101 MHz, CDCN): δ 10.8 (*C*H$_3$), 25.6 (*C*H$_2$), 46.7 (*C*H), 55.0 (*C*H$_3$), 57.7 (*C*H$_3$), 57.7 (*C*H), 68.2 (*C*H), 110.1 (*C*H), 110.2 (*C*H), 113.1 (*C*H), 114.2 (2C, *C*H), 115.0 (2C, *C*H), 125.7 (*C*H), 127.7 (2C, *C*H), 128.3 (2C, *C*H), 133.1 (*q*), 141.7 (q), 142.9 (q), 144.6 (q), 151.7 (q), 152.6 (q); IR ν_{max} (neat) 3360, 2931, 1510 cm^{-1}; HRMS (CI) calcd for $C_{25}H_{28}N_2O_2^+$, [M^+] 388.2145 found 388.2151.

Entry 5 (1*S,2*S**,1′*R**)-*N*-(4-methoxyphenyl)-6-methyl-2-(1′-phenylpropyl)indolin-3-amine.** Light yellow oil (62%); ^{1}H NMR (400 MHz, CDCN): δ 0.70 (3H, t, J = 7.4), 1.66 (1H, ddq, J = 13.4, 11.5, 7.3), 1.83–1.92 (1H, m), 2.21 (3H, s), 2.93–3.09 (1H, m), 3.65 (3H, s), 3.83–4.02 (2H, m), 4.28 (1H, app. t, J = 8.2), 4.74 (1H, br. s), 6.23–6.32 (2H, m), 6.36 (1H, d, J = 7.5), 6.53 (1H, s), 6.56–6.67 (2H, m), 6.72–6.82 (1H, m), 7.10–7.28 (5H, m); ^{13}C NMR (101 MHz, CDCN): δ 10.8 (*C*H$_3$), 20.4 (*C*H$_3$), 25.5 (*C*H$_2$), 46.7 (*C*H), 54.9 (*C*H$_3$), 57.0 (*C*H), 67.8 (*C*H), 110.3 (*C*H), 114.1 (2C, *C*H), 114.8 (2C, *C*H), 118.6 (*C*H), 123.2 (*C*H), 125.7 (*C*H), 127.7 (2C, *C*H), 128.3 (2C, *C*H), 129.0 (*q*), 138.0 (q), 141.8 (q), 142.9 (q), 151.0 (q), 151.6 (q); IR ν_{max} (neat) 3365, 2929, 1511, 1236 cm^{-1}; HRMS (EI) calcd for $C_{25}H_{26}N_2O^+$, [M^+] 372.2196 found 372.2207.

Entry 7 (1*S,2*S**,1′*R**)-*N*-(4-methoxyphenyl)-2-(1′-*p*-tolylpropyl)indolin-3-amine.** Oil, (64%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81 (3H, t, J = 7.3), 1.77 (1H, ddq, J = 13.1, 11.5, 7.3), 1.65 (1H, dqd, J = 13.1, 7.3, 3.6), 2.37 (3H, s), 3.02–3.19 (1H, m), 3.40 (1H, br. s), 3.75 (3H, s), 3.94 (1H, dd, J = 9.8, 6.5), 4.16 (1H, m), 4.34 (1H, d, 6.5), 6.19–6.32 (2H, m), 6.60–6.72 (3H, m), 6.75 (1H, d, J = 7.8), 6.94 (1H, d, J = 7.3), 7.05–7.18 (5H, m); ^{13}C NMR (101 MHz, CDCN): δ 11.8 (*C*H$_3$), 21.0 (*C*H$_3$), 25.9 (*C*H$_2$), 46.3 (*C*H), 55.7 (*C*H$_3$), 59.0 (*C*H), 68.8 (*C*H), 110.1 (*C*H), 114.5 (2C, *C*H), 116.3 (2C, *C*H), 119.1 (*C*H), 124.1 (*C*H), 128.5 (2C, *C*H), 128.6 (*C*H), 128.9 (2C, *C*H), 131.9 (q), 135.6 (q), 139.4 (q), 141.7 (q), 150.0 (q), 152.4 (q); IR ν_{max} (neat) 3408, 2928, 1510 cm^{-1}; HRMS (EI) calcd for $C_{25}H_{28}N_2O^+$, [M^+] 372.2196 found 372.2203.

Entry 8 (1*S,2*S**,1′*R**)-*N*-(4-methoxyphenyl)-2-(1′-*o*-tolylpropyl)indolin-3-amine.** Off white solid (66%) m.p. 55–57 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.60 (3H, t, J = 7.3), 1.52–1.70 (1H, m), 1.89–1.99 (1H, m), 2.39 (3H, s), 3.32–3.50 (1H, m), 3.71 (3H, s), 3.79–3.96 (2H, m), 4.22 (1H, br. d, J = 11.1), 4.96 (1H, dd, J = 11.0, 6.9), 6.46 (1H, d, J = 7.8), 6.49–6.75 (1H, m), 6.72–6.84 (4H, m), 6.91–6.99 (1H, m), 7.03 (1H, d, J = 7.3), 7.11–7.18 (1H, m), 7.19–7.28 (2H, m), 7.29–7.38 (1H, m); ^{13}C NMR (101 MHz, CDCN): δ 10.4 (*C*H$_3$), 19.4 (*C*H$_3$), 26.1 (*C*H$_2$), 40.6 (*C*H), 54.9 (*C*H$_3$), 56.3 (*C*H), 68.0 (*C*H), 109.5 (*C*H), 114.4 (2C, *C*H), 115.3 (2C, *C*H), 117.6 (*C*H), 123.8 (*C*H), 125.6 (*C*H), 125.9 (*C*H), 126.2 (*C*H), 128.1 (*C*H), 129.8 (*C*H, 131.7 (q), 137.5 (q), 141.3 (q), 141.8 (q), 150.5 (q), 151.9 (q); IR ν_{max} (neat) 3365, 2929, 1511, 1236 cm^{-1}; HRMS (CI) calcd for $C_{25}H_{27}N_2O^+$, [M + H$^+$] 373.2280 found 373.2285.

Entry 9 (1*S,2*S**,1′*R**)-2-(1′-(4-fluorophenyl)propyl)-*N*-(4-methoxyphenyl)indolin-3-amine.** Oil (70%); ^{1}H NMR (400 MHz, CDCN): δ 0.50 (3H, t, J = 7.3), 1.35–1.49 (1H, m), 1.63–1.72 (1H, m), 2.81 (1H, app td, J = 10.6, 3.5), 3.45 (3H, s), 3.71 (1H, ddd, J = 10.0, 6.9, 3.3), 3.77 (1H, d, J = 10.6), 4.11 (1H, dd, J = 10.5, 6.9), 4.64 (1H, m, J = 2.0), 6.05–6.14 (2H, m), 6.29–6.36 (1H, m), 6.38–6.45 (2H, m), 6.50 (1H, d, J = 7.8), 6.68 (1H, d, J = 6.8), 6.70–7.06 (5H, m); ^{13}C NMR (101 MHz, CDCN): δ 12.1 (*C*H$_3$), 27.1 (*C*H$_2$), 47.3 (*C*H), 56.2 (*C*H$_3$), 58.4 (*C*H), 68.9 (*C*H), 111.0 (*C*H), 115.4 (d, J_{CF} = 21.6, 2C, *C*H), 115.5 (3C, *C*H), 119.2 (2C, *C*H), 124.8 (*C*H), 129.5 (*C*H), 131.2 (d, J_{CF} = 8.0, 2C, *C*H), 132.9 (q), 140.2 (d, J_{CF} = 3.2, q), 143.0 (q), 152.1 (q), 153.0 (q), 162.3 (d, J_{CF} = 241.3, q); ^{19}F NMR (376 MHz, CDCN) δ_F −119.1 (s); IR ν_{max} (neat) 3366, 2931, 1510 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{25}FN_2O^+$, [M^+] 376.1945 found 376.1940.

9 (1*R,2*S**)-*N*-(1-(2-Bromophenyl)-2-nitro-3-phenylpropyl)-4-methoxyaniline.**[38] Yellow solid (68%) m.p. 105–107 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.19 (1H, app. d, J = 14.7), 3.48 (1H, dd, J = 15.0, 11.4), 3.71 (3H, s), 4.52 (1H, br. s), 5.36 (1H, ddd, J = 11.4, 5.0, 2.8), 5.40 (1H, d, J = 5.0), 6.55 (2H, d, J = 8.8), 6.69–6.78 (2H, m), 7.09 (2H, d, J = 7.3), 7.19–7.32 (5H, m), 7.48 (1H, d, J = 8.1), 7.65 (1H, d, J = 8.1); ^{13}C NMR (151 MHz, $CDCl_3$): δ 33.9 (*C*H$_2$), 55.6 (*C*H$_3$), 60.9 (*C*H), 90.9 (*C*H), 114.8 (2C, *C*H), 115.7 (2C, *C*H), 123.1 (q), 127.3 (*C*H), 128.1 (*C*H), 128.6 (2C, *C*H), 128.8 (2C, *C*H), 129.5 (*C*H), 130.1 (*C*H), 133.8 (*C*H), 135.5 (q), 136.1 (q), 139.5 (q), 153.2 (q); IR ν_{max} (neat) 3395, 2934, 1549, 1236 cm^{-1}; HRMS (ES) calcd for $C_{22}H_{22}BrN_2O_3^+$, [M + H$^+$] 441.0809 found 441.0808.

10 (1*R,2*S**)-2-Benzyl-*N*-(4-methoxyphenyl)indolin-3-amine.** Prepared by the 'General Procedure for the synthesis of indoline 7'. Off white solid (75%), m.p. 83–85 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.81 (1H, dd, J = 13.4, 9.4), 3.05 (1H, dd, J = 13.4, 4.8), 3.67 (1H, br. s), 3.80 (3H, s), 3.85 (1H, br. s), 3.87 (1H, app. dt, J = 9.3, 4.7), 4.77 (1H, dd, J = 4.4), 6.55 (2H, dd, J = 8.8), 6.65 (1H, dd, J = 7.7), 6.73–6.83 (3H, m), 7.16 (1H, t, J = 7.7), 7.22–7.34 (4H, m), 7.34–7.42 (2H, m); ^{13}C NMR (151 MHz, CDCN): δ 41.0 (*C*H$_2$), 55.8 (*C*H$_3$), 61.8 (*C*H), 66.8 (*C*H), 109.9 (*C*H), 115.0 (2C, *C*H), 115.0 (2C, *C*H), 118.8 (*C*H), 125.5 (*C*H),

126.6 (*C*H), 128.7 (2C, *C*H), 129.2 (q), 129.3 (*C*H), 129.3 (2C, *C*H), 138.5 (q), 141.2 (q), 149.9 (q), 152.4 (q); IR ν_{max} (neat) 3373, 2932, 1510 cm^{-1}; HRMS (EI) calcd for $C_{25}H_{28}N_2O^+$, $[M^+]$ 330.1732 found 330.1741.

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