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

James C. Anderson,*a Ian B. Campbell,b Sebastien Campos,b Jonathan Shannona and Derek A. Tocher†a

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 carbylons,11–13 peptidomimetics,14 natural products15–20 and many heterocyclic small molecules21–32 of importance to drug discovery. The anti-diastereoisomer dominates with higher homologues of nitrromethane, 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 zines 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 ZnEt2 (1.1 equiv.) as judged by TLC. The resultant nitratone 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 1H 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.

§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.

Properties and Characterisation

1H and 13C NMR data were recorded for each compound on a Bruker Avance DPX 200 (200 MHz for 1H and 50 MHz for 13C) spectrometer. Spectral assignment was aided by 1D and 2D homonuclear experiments (HSQC, HMBC). Suitable solvents were selected to minimise spectral overlap and allow clean assignments. The chemical shift (δ) values are reported in parts per million (ppm) and the coupling constants (J) in hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.
A screen of different protecting groups of the imine partner 2 (COPh, CO₂Bn, PO₃Ph) along with various Lewis and Bronsted acid promoters in place of TFA (AcOH, CF₃SO₃H, MeSO₃H, Yb(OTf)₃, AlCl₃, Zn(OTf)₂, BF₃·Et₂O) 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 diastereomer 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

³⁶A 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 diastereoisomer being stable to purification, so most probably has the syn-relative stereochemistry across the nitro-amine bond.
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 Et₂O gave the highest diastereoselectivity followed by toluene (80:20), which contained more side products and unlike Et₂O 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. 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.†

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). Although the nitro group was completely reduced, a 1:1 mixture of the desired amine 5bb and the debranched 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. However, as the syn,syn-diastereoisomers like 3bb are in general inert to trifluoroacetylation, 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[PPh₃]₄ Buchwald–Hartwig conditions that we have used to perform analogous cyclisations (Scheme 1), 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'Bu 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 substituent 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 diastereoselectivites 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, 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[PPh₃]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[PPh₃]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, also lead 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. 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, 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 zins that can be derived from the tandem hydroboration/boron-zinc exchange method developed by Knochel, it would
benzylzinc bromide and allylzinc bromide both gave low dia-
addition nitro-Mannich reaction38,44 and with these particular
selectivity (60 : 40). (Scheme 8), but unfortunately a significant drop in diastereo-
to ethylmagnesium bromide gave an optimised yield of 70%
not successful with vinyl magnesium bromide, but changing
conjugate addition stage. Exploration of Grignard reagents was
reaction mixture.

Table 1 Scope of indoline formationa

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<th>Entry</th>
<th>Ar1</th>
<th>Ar2</th>
<th>3 dr crudeb (%)</th>
<th>Yield 3c (%)</th>
<th>Yield 2c (%)</th>
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<td>Ph</td>
<td>2-BrPh</td>
<td>85 : 15</td>
<td>68</td>
<td>64</td>
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<tr>
<td>2</td>
<td>Ph</td>
<td>2-Br-5-FPh</td>
<td>90 : 10</td>
<td>72</td>
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<tr>
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<td>Ph</td>
<td>2-Br-5-MeOPh</td>
<td>80 : 20</td>
<td>63</td>
<td>40</td>
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<td>Ph</td>
<td>2-Br-4,5-(MeO)2Ph</td>
<td>80 : 20</td>
<td>57</td>
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<tr>
<td>5</td>
<td>Ph</td>
<td>2-Br-4-MePh</td>
<td>85 : 15</td>
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<tr>
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<td>2-Br-3-pyridinyl</td>
<td>80 : 20</td>
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<td>80 : 20</td>
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<td>66</td>
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<td>4-FPh</td>
<td>2-BrPh</td>
<td>75 : 25</td>
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a Nitro-Mannich: 1 (3 mmol), Cu(OTf)2 (5 mol%), ZnEt2 (1.1 equiv.), Et2O, −78 °C, 5 min, then RT 2 h; 2 (1.1 equiv.), Et3O, −78 °C, 10 min; TFA (2.6 equiv.), Et3O, −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 4 in PPh3 (1.5 mL) added to NaOEtBu (1.00 mmol), Pd[PPh3]4 (0.025 mmol) in PhMe (1 mL) at RT then 90 °C, 16–24 h.
b Diastereoselectivities were calculated by comparison of the 1H NMR signals for the CHNCHO 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.

be better if more readily available carbon nucleophiles could be found. In an attempt to widen the scope of the reaction to include organozinc halides42,43 test reactions revealed that benzylzinc bromide and allylzinc bromide both gave low dia-
stereselectivities and trace conversions (<10%) with 1b and 2b in THF and Et3O. 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 diastereo-
selectivity (60 : 40).

We have found nucleophilic hydride useful in the conjugate addition nitro-Mannich reaction38,44 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 indole 10 in 75% yield from 9 (Scheme 9). The sense of diastereo-
selection 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 intramolecu-
lar 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-nitro-
amine 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 organ-
zinc halides, a limitation to the current methodology is that dialkyl zinc species are the most e

| Scheme 7 Scope of indoline formation. |

| Scheme 8 Use of Grignard nucleophile. |

| Scheme 9 Sequence using the reductive nitro-Mannich reaction. |

[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$_2$O (5 mL) at -78 °C was added Et$_3$Zn (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$_2$O (5 mL) was added and the mixture stirred for 10 min. Then a solution of TFA (7.8 mmol) in Et$_2$O (0.2 mL) was added dropwise over 20 s and the reaction stirred for 1 h. The reaction was warned 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$_2$O and saturatedaq. NaHCO$_3$. The layers were separated, and the aqueous phase was extracted with Et$_2$O. The organic layers were combined, and the solvent was removed in vacuo to provide crude β-nitroamine. Diastereoselectivities were calculated by comparison of the 1H NMR signals for the CHCHNO$_2$ protons (δ 3.1–3.6 ppm). Purification by flash chromatography yielded diastereomerically pure syn,syn-β-nitroamines 3.

**syn,anti-4aa (1R*,2S*,3R*)-N-(1-(2-Bromomethyl)-2-nitro-3-phenylpentyl)-4-methoxybenzenamine.** Yellow solid (72%) m.p. 123–124 °C; 1H NMR (600 MHz, CDCl$_3$): δ 0.76 (3H, t, $J = 7.3$), 1.63 (1H, ddq, $J = 13.4, 7.3, 3.5$), 1.80 (1H, ddq, $J = 13.4, 11.6, 7.3$), 2.90 (1H, td, $J = 11.4, 3.5$), 3.20 (2H, m), 4.50 (1H, dd, $J = 10.2, 3.3$), 5.05 (1H, dd, $J = 11.4, 3.3$), 5.22 (1H, d, $J = 11.4, 3.3$), 6.19–6.22 (2H, m), 6.80 (1H, ddd, $J = 8.6, 7.6, 3.0$), 7.16 (1H, ddd, $J = 9.2, 3.0, 3.0$), 7.24–7.30 (5H, m), 7.43 (1H, dd, $J = 8.6, 5.0$); 13C NMR (126 MHz, CDCl$_3$): δ 14.2 (CH$_3$), 25.1 (CH$_2$), 48.3 (CH), 55.7 (CH$_3$), 56.2 (CH), 95.2 (CH), 114.3 (2C, CH), 114.9 (2C, CH), 115.0 (d, $J_{CF} = 24.2$, CH), 116.9 (d, $J_{CF} = 2.7$, q), 117.2 (d, $J_{CF} = 22.9$, CH), 128.0 (CH), 128.9 (2C, CH), 129.0 (2C, CH), 134.5 (d, $J_{CF} = 7.7$, CH), 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 $\nu_{max}$ (neat) 3417, 2966, 1550, 1242 cm$^{-1}$; HRMS (EI) calcd for C$_{24}$H$_{23}$BrN$_2$O$_4$, [M]$^+$ 486.0948 found 486.0934; Anal. calcd for C$_{24}$H$_{23}$BrN$_2$O$_4$: C, 59.13; H, 4.96; N, 5.75; found: C, 59.09; H, 4.89; N, 5.78%.

**Entry 3 (1S*,2S*,3R*)-N-(1-(2-bromo-5-methoxyphenyl)-2-nitro-3-phenylpentyl)-4-methoxybenzenamine.** Yellow solid (63%) m.p. 148–150 °C; 1H NMR (400 MHz, CDCl$_3$): δ 0.75 (3H, t, $J = 7.3$), 1.63 (1H, ddq, $J = 13.5, 7.3, 3.5$), 1.80 (1H, ddq, $J = 13.5, 11.3, 7.3$), 2.27–2.36 (6H, m), 3.66 (3H, s), 4.67 (1H, m), 4.76 (1H, ddd, $J = 11.3, 3.5, 3.5$), 5.20 (1H, br. s), 6.15–6.28 (2H, m), 6.56–6.69 (4H, m), 7.21–7.39 (6H, m); 13C NMR (101 MHz, CDCl$_3$): δ 11.6 (CH$_3$), 25.2 (CH$_2$), 48.2 (CH), 55.3 (CH$_3$), 56.2 (CH), 95.5 (CH), 113.1 (q), 113.6 (q), 114.3 (2C, CH), 114.8 (2C, CH), 115.2 (CH), 127.8 (CH), 128.7 (2C, CH), 128.9 (2C, CH), 133.7 (CH), 137.1 (q), 138.0 (q), 139.5 (q), 152.3 (q), 159.5 (q); IR $\nu_{max}$ (neat) 3406, 2935, 1550, 1240 cm$^{-1}$; HRMS (ES) calcd for C$_{24}$H$_{23}$BrN$_2$O$_4$, [M$^+$ + H]$^+$ 499.1232 found 499.1236.

**Entry 4 (1S*,2S*,3R*)-N-(1-(2-bromo-4,5-dimethoxyphenyl)-2-nitro-3-phenylpentyl)-4-methoxybenzenamine.** Yellow solid (57%) m.p. 53–55 °C; 1H NMR (600 MHz, CDCl$_3$): δ 0.75 (3H, t, $J = 7.3$), 1.62 (1H, ddq, $J = 13.5, 7.3, 3.5$), 1.79 (1H, ddq, $J = 13.5, 11.7, 7.3$), 2.60 (1H, td, $J = 11.4, 3.5$, 3.5), 3.67 (3H, s), 3.69 (3H, s), 3.80 (3H, s), 4.15 (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); 13C NMR (126 MHz, CDCl$_3$): δ 11.7 (CH$_3$), 25.2 (CH$_2$), 48.3 (CH), 55.7 (CH$_3$), 56.1 (CH), 56.2 (CH), 95.9 (CH), 109.8 (CH), 114.4 (2C, CH), 114.9 (2C, CH), 115.6 (CH), 127.9 (CH), 128.8 (2C, CH), 128.9 (2C, CH), 134.5 (CH), 137.2 (q), 139.6 (q), 149.0
Entry 5 (1S,2S,3R*)-N-(1-(2-bromophenyl)-2-nitro-3-pentyl)-4-methoxybenzenamine. Yellow solid (63%) m.p. 97–99 °C; 1H NMR (400 MHz, CDCl3); δ 0.75 (3H, t, J = 7.3), 1.63 (1H, ddq, 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); 13C NMR (101 MHz, CDCl3); δ 11.6 (CH2), 20.6 (CH3), 48.2 (CH), 55.6 (CH3), 55.8 (CH), 95.7 (CH), 114.4 (2CH), 114.8 (2CH2, 122.8 (q), 127.0 (CH), 127.8 (CH), 128.7 (2C, CH), 128.9 (2C, CH), 128.9 (CH), 133.6 (CH), 133.7 (q), 137.2 (q), 139.5 (q), 152.3 (q); IR υmax (neat) 3415, 2932, 1550, 1243 cm−1; HRMS (ES) calcd for C23H25BrN3O3, [M + H]+ 483.1278 found 483.1283.

Entry 6 (1S,2S,3R*)-N-(1-(2-bromopyridin-3-yl)-2-nitro-3-pentyl)-4-methoxybenzenamine. Yellow solid (55%) m.p. 143–145 °C; 1H NMR (400 MHz, CDCl3); δ 0.75 (3H, t, J = 7.3), 1.63 (1H, ddq, 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); 13C NMR (101 MHz, CDCl3); δ 11.6 (CH), 25.2 (CH2), 48.1 (CH), 55.6 (CH3), 55.7 (CH3), 95.1 (CH), 114.3 (2CH), 115.0 (2C, CH), 123.5 (CH), 128.0 (CH), 128.7 (2C, CH), 128.8 (2C, CH), 134.7 (q), 136.1 (CH), 136.8 (q), 138.8 (q), 142.8 (q), 149.7 (CH), 152.6 (q); IR υmax (neat) 3414, 2934, 1548, 1241 cm−1; HRMS (ES) calcd for C24H23BrN2O3+, [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-nitroaniline (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. NaHCO3. 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 (1.5 ml). The reaction vessel was heated at 90 °C until the reaction was complete by TLC analysis (approximately 1 h). The reaction was quenched by the addition of EtOAc and saturated aq. NaHCO3. 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 (1.0 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 (NH2) silica yielded the indoline 7 (Table 1).

7b Entry 1 (1S,2S*,3R*)-N-(1-(2-bromophenyl)-2-nitro-3-pentyl)-4-methoxybenzenamine. Yellow oil (64%); 1H NMR (600 MHz, CD2Cl2); δ 0.75 (3H, t, J = 7.3), 1.65 (1H, ddq, J = 13.1, 7.3, 3.6), 3.10 (1H, ddd, J = 11.3, 4.3, 7.8), 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); 13C NMR (151 MHz, CD2Cl2); δ 10.7 (CH3), 24.9 (CH2), 45.7 (CH), 53.8 (CH3), 57.9 (CH), 67.5 (CH), 109.1 (CH), 113.5 (2C, CH), 115.4 (2C, CH), 118.0 (CH), 123.1 (CH), 127.1 (2C, CH), 127.5 (CH), 127.7 (2C, CH), 131.1 (q), 140.5 (q), 141.6 (q), 149.2 (q), 151.8 (q); IR υmax (neat) 3367, 2928, 1243 cm−1;
HRMS (ES) caleld for C$_2$H$_{28}$N$_2$O$_2^+$, [M$^+$] 358.2040 found 358.208.

Entry 2 (15S,2S*,1'R)-5-fluroo-N-(4-methoxyphenyl)-2-(1'-
phenylpropyl)indolin-3-amine. Yellow oil (53%); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.72 (3H, t, $J = 7.4$), 1.66 (1H, dqq, $J = 13.1, 11.5, 7.3$), 1.88–1.94 (1H, m), 3.02 (1H, app. t, $J = 9.8$), 4.30 (1H, br. s), 1.44 (1H, dd, $J = 13.1, 3.6$), 2.37 (3H, s), 2.93–3.09 (1H, m), 3.56 (3H, s), 3.84 (2H, m), 5.40 (1H, app. t, $J = 9.8$), 6.95 (1H, m), 7.12–7.20 (5H, m); $^13$C NMR (101 MHz, CDCl$_3$): $\delta$ 10.8 (CH$_3$), 25.6 (CH$_2$), 46.7 (CH), 55.0 (CH$_3$), 57.7 (CH), 68.2 (CH), 110.1 (CH), 112.0 (CH), 113.1 (CH), 114.2 (2C, CH), 115.0 (2C, CH), 125.7 (CH), 127.7 (2C, CH), 128.3 (2C, CH), 129.0 (q), 138.0 (q), 141.8 (q), 142.9 (q), 151.0 (q), 151.6 (q); IR $\nu_{max}$ (neat) 3435, 2929, 1511, 1316 cm$^{-1}$; HRMS (ES) caleld for C$_{23}$H$_{28}$BrN$_2$O$_2^+$, [M$^+$ + Br$^-$] 441.0809 found 441.0808.

10 (1R*,2S*)-2-Benzyl-N-(4-methoxyphenyl)indolin-3-amine. Prepared by the 'General Procedure for the synthesis of indole 7'. Off white solid (75%), m.p. 83–85 °C; $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 3.21 (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 (2H, m), 7.16 (1H, $J = 7.7$), 7.22–7.34 (4H, m), 7.34–7.42 (2H, m); $^1$C NMR (151 MHz, CDCl$_3$): $\delta$ 41.0 (CH$_3$), 55.8 (CH$_2$), 61.8 (CH), 66.8 (CH), 109.9 (CH), 115.0 (2C, CH), 115.0 (2C, CH), 118.8 (CH), 125.5 (CH), 128.5 (2C, CH), 128.6 (2C, CH), 131.9 (q), 135.6 (q), 139.4 (q), 141.7 (q), 150.0 (q), 152.4 (q); IR $\nu_{max}$ (neat) 3408, 2928, 1510 cm$^{-1}$; HRMS (EI) caleld for C$_{23}$H$_{28}$N$_2$O$_2^+$, [M$^+$] 372.2196 found 372.2203.
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References