Reductive Conjugate Addition nitro-Mannich Route for the Stereoselective Synthesis of 1,2,3,4-Tetrahydroquinoxalines

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Abstract. A concise, high yielding and structurally divergent synthesis of complex 1,2,3,4-tetrahydroquinoxalines with excellent diastereoselectivity is described. A wide array of nitroalkenes and imines derived from commercially available aromatic aldehydes and 2-chloroanalines were subjected to a key reductive conjugate addition nitro-Mannich reaction to give diastereomerically pure β-nitro amines. Sequential reduction of the nitro function followed by Pd-catalyzed intramolecular *N*-arylation of the resultant primary amine onto the 2-chloroanailine gives highly substituted 1,2,3,4-tetrahydroquinoxalines. Non basic imines were found to participate better in the nitro-Mannich reaction if the stronger acid methanesulfonic acid was used to promote the reaction. The 3 step reaction sequence should be useful for the array synthesis of drug like scaffolds.

Introduction.

The 1,2,3,4-tetrahydroquinoxaline scaffold has become increasingly important in medical chemistry.[1] Several compounds containing the 1,2,3,4-tetrahydroquinoxaline core have demonstrated biological activities against a range of targets including as

potent cholesteryl ester transfer protein inhibitors,[1a] vasopressin V2 receptor antagonists,[1b] and prostaglandin D2 receptor antagonists,[1c] (Figure 1). Despite the marked interest in 1,2,3,4-tetrahydroquinoxalines there are only a limited number of synthetic methods available.[2] The most common approach for the synthesis of tetrahydroquinoxalines is the hydrogenation of quinoxalines.

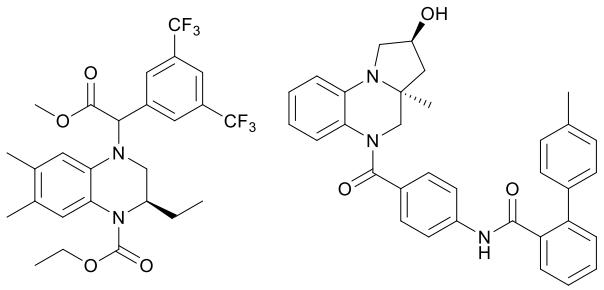
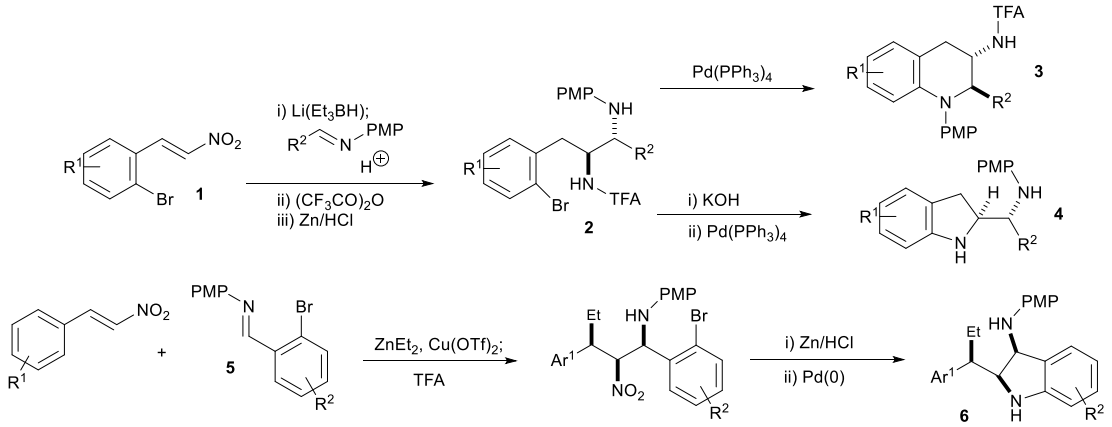


Figure 1: Biologically active 1,2,3,4-tetrahydroquinoxalines.

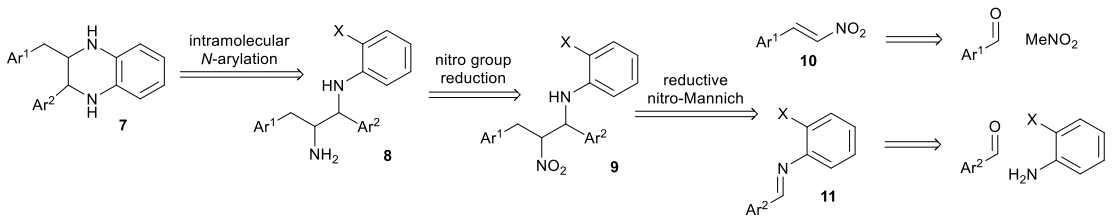
We have investigated the use of the nitro-Mannich reaction[3] in the synthesis of stereochemically defined heterocyclic ring systems.[4] In order to access more complex heterocycles we have expanded the structures of possible nitroalkane reaction partners through the *in situ* conjugate addition of nucleophiles to nitroalkenes, with trapping of the subsequent nitronate species with an imine partner.[5] We have shown that this procedure can be used to generate more complex stereodefined β-nitroamines that can be used in heterocycle synthesis.[6] 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.[7] We have shown that the reductive nitro-Mannich reaction with arylbromide nitrostyrenes **1** can deliver stereodefined functionalised diamine building blocks **2** that are precursors to either 3-aminotetrahydroquinolines **3** or 2-aminomethylene indolines **4** via *N*-arylation (Scheme 1).[7a] More recently we demonstrated that placing the *N*-arylation cyclisation handle on the imine precursor **5**, derived from an *ortho*-bromine substituted aromatic aldehyde gave 1,2-diamine containing indolines **6** (Scheme 1).[7b] In this paper we detail an alternative combination leading to the stereoselective synthesis of an array of 1,2,3,4-tetrahydroquinoxalines **7** (Scheme 2). Disconnection of **7** using a key *N*-arylation leads to diamine **8** which can be derived from reduction of β-nitroamine **9**. This can be accessed from a stereoselective reductive nitro-Mannich reaction[5a,b] between

nitroalkene **10** and imine **11**. In this combination the *N*-arylation cyclisation handle is part of the aryl amine of the imine **11**. The nitroalkenes can be prepared from a Henry reaction and the imine from an *ortho*-halo amine and aldehyde. An important feature of the strategy is the ease in which structural diversity can be introduced into the products. This arises from the large selection of aromatic aldehydes that can be used to form nitroalkene **10**, as well as the *ortho*-halo amines and aldehydes used to form imine **11**. This provides the opportunity for the synthesis of an array of novel fused heterocyclic structures which we exemplify here.

Scheme 1. Previous work



Scheme 2. This work



Results and discussion

The first step in the synthetic strategy was the one-pot reductive nitro-Mannich reaction between nitrostyrenes **10** and imines **11** which was performed with lithium triethylborohydride according to our previously published procedure,[5b] furnishing β-nitroamines **9** in excellent conversion and diastereoselectivity (Scheme 3, Table 1).

Scheme 3. Stereoselective reductive nitro-Mannich reaction

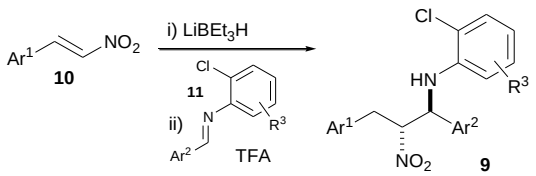
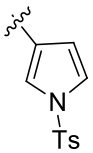
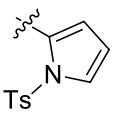


Table 1. Scope of β-nitroamine[a]

Product	Ar^1	Ar^2	R^3	Conversion (%)	**9** *dr* crude[b]	Yield **9** (%)[c]
9a	Ph	Ph	H[d]	>95	90:10	68
9b	Ph	Ph	H	>95	95:5	72
9c	4-MePh	Ph	H	>95	90:10	75
9d	2-MePh	Ph	H	>95	90:10	70
9e	4-MeO-Ph	Ph	H	>95	90:10	74
9f	2-MeO-Ph	Ph	H	>95	85:15	71
9g	3-py	Ph	H	>95	>95:5	67
9h	Ph	Ph	4-*t*Bu	>95	90:10	79
9i	Ph	Ph	4-F	>95	90:10	65
9j	Ph	Ph	4-OMe	>95	85:15	72
9k	Ph	Ph	6-Me	45	55:45	—[e]
9l	Ph	Ph	5-CF_3	50	90:10	—[e]
9m	Ph	Ph	3-py[f]	>95	90:10	61
9n	Ph	3-MeO-Ph	H	>95	95:5	72
9o	Ph	3-CF_3-Ph	H	>95	90:10	63[g]
9p	Ph	2-Me-Ph	H	>95	80:20	—[g]
9q	Ph	3-furyl	H	>95	75:25	70
9r	Ph	3-py	H	40[h]	90:10	—[e]
9s	Ph		H	>95	80:20	—[i]
9t	Ph		H	>95	80:20	—[i]

[a]Nitro-Mannich: **10** (3 mmol), superhydride® (1.05 equiv. 1M in THF), CH_2Cl_2, rt, 1h; **11** (1.5 equiv.), TFA (2.6 equiv.), CH_2Cl_2, -78 °C, 1h then rt 1h. [b]Diastereoselectivities were calculated by comparison of the ^{1}H NMR signals for the CH_2CHNO_2 protons (~δ 3.1-3.6 ppm) of the crude reaction mixture.

[c]Isolated yield of pure *anti*-diastereoisomer. [d]2-Br instead of 2-Cl. [e]Reaction not purified. [f]Imine derived from 3-amino-2-chloropyridine. [g]Diastereoisomers inseparable. [h]TFA (2.6 equiv.). [i]Decomposed on silica chromatography.

The β-nitroamines **9** were tentatively assigned the *anti*-stereochemistry based upon the 1H NMR chemical shifts (δ) and coupling constants (J) recorded for the protons adjacent to the two nitrogen atoms. In our nitro-Mannich system the vast majority of products have given *anti*-selectivity, for which we have forwarded a transition state model.[8,9] The assignment of these β-nitroamines **9** was corroborated by single crystal X-ray analysis of a derivative of **9b** (see ESI). Due to the relative instability of β-nitroamines these products are usually isolated as their trifluoroacetamides, by treatment of the crude reaction mixtures with TFAA in the presence of pyridine. Unusually these particular β-nitroamines (**9**) were relatively stable to silica chromatography and could be isolated as single diastereoisomers and used directly in the next steps of the reaction sequence towards the 1,2,3,4-tetrahydroquinoxalines **7**.

The Nitrostryene component **10** had the broadest compatibility (Ar^1), with electron rich, electron deficient and a pyridyl group all showing good conversion and diastereoselectivity (**9a**-**g**). A 2-halo substituent was necessary in the aniline group to enable an *N*-arylation cyclisation. Although the *ortho*-bromoanailine derived imine worked well in this nitro-Mannich reaction (**9a**), there was a wider diversity of anilines available that possessed the *ortho*-chloro substituent (R^3). The *ortho*-chloroanilines were found to be able to tolerate, sterically bulky, electron rich and electron deficient substituents as well as a nitrogen containing heterocycle (Entries **9h**-**j**, **9m**) in this reaction. The reaction struggled with conversion when there was steric congestion close to the imine (**9k**) and gave virtually no diastereoselectivity. The deactivating 5-CF_3 substituent reduced conversion to ~50% (**9l**), but gave good diastereoselectivity. The most sensitive component to change was the aromatic aldehyde substituent of the imine **11** (Ar^2), which tolerated some electron donating (**9n**), electron withdrawing (**9o**) substituents, but gave either a low conversion or diastereoselectivity with 2-substituents (**9p**) and heterocyclic rings (**9q**-**t**). The diastereoisomers of product **9o** derived from 3-trifluorobenzaldehyde could not be

separated and were isolated as a 90:10 mixture. Similarly the diastereoisomers of product **9p** derived from 2-methylbenzaldehyde could not be separated and due to the poorer diastereoselectivity (80:20) was not investigated further. The products derived from the *N*-tosylpiperidine imines (**9s**,**t**) were unstable towards chromatography.

It was notable that lower conversion was observed when the substituent of the imine could affect the pK_aH of the imine (for example **9l** and **9r**). Previous nitro-Mannich reactions from our work have demonstrated that the imine partner needs to be protonated for these particular nitro-Mannich reactions, that is with an alkyl or aryl substituent on the nitrogen of the imine, to proceed.[8,7b] The pK_aH(H_2O) of several imines were measured in order to probe this phenomenon more accurately (See ESI). The PMP protected imine **12** works well in nitro Mannich reactions[7b] and has a pK_aH 5.4. The standard 2-chloroaniline derived imine **11b** has pK_aH 2.8 and appears to function well in this reaction (Table 1, **9b**). The 2-chloro-5-trifluoromethylaniline derived imine **11l** has pK_aH <2.0 and only gave 50% conversion under our standard conditions with TFA (Table 1, **9l**). This is in contrast to having the trifluoromethyl group on the aldehyde portion of the imine. Imine **11o** has pK_aH 2.7 and functions well in these reactions (**9o**). Imine **11r** derived from pyridine-3-carboxaldehyde has pK_aH 2.9, but due to the pyridine group. Presumably under the acidic conditions the pyridine is protonated and this has an adverse effect on the basicity of the imine lone pair, significantly reducing conversion to 40% with TFA (Table 1, **9r**). In an attempt to improve conversion, other acids were screened in the reductive nitro-Mannich reaction (Scheme 3 and Table 2), with imine **11r**. It was found that the stronger acid $MeSO_3H$ gave the best result for imine **11r** with a 64% yield of pure anti-β-nitroamine **9r** isolated. In this case at least two equivalents of $MeSO_3H$ were required for complete conversion. This suggested that the pyridine nitrogen is protonated first, which lowers the pK_aH of the imine nitrogen, and therefore a stronger acid is required to protonate the imine nitrogen. Imine **11l** with $MeSO_3H$ gave a much improved conversion (>95%) compared to only 50% with TFA (Table 1), resulting in a 61% isolated yield of **9l**, but as a 90:10 mixture of diastereoisomers. The diastereoselectivity remained unaltered, as it also did for the imine **11q** derived from furan-3-carboxaldehyde (cf Table 1, **9q**).

Figure 2. $pK_a(H_2O)$ of selected imines

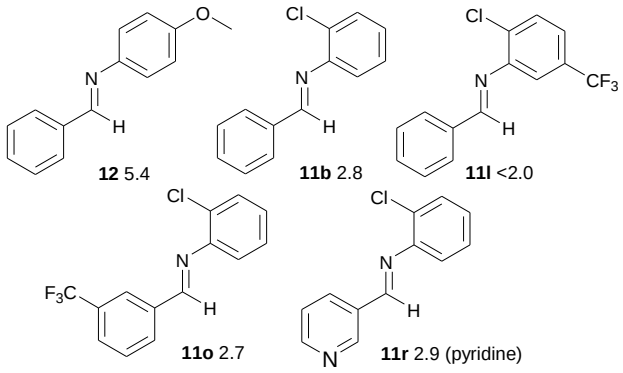


Table 2. Effect of acid on reductive nitro-Mannich reaction[a]

Imine	Acid	Conversion (%)	**9** *dr* crude[b]	Yield **9** (%)
11r	TFA	40	90:10	—[c]
11r	AcOH	0	—	—
11r	Citric	0	—	—
11r	$MeSO_3H$	>95	95:5	64[d]
11r	CF_3SO_3H	>95	90:10	50[d]
11r	HCO_2H	35	85:15	—[c]
11r	Maleic	30	85:15	—[c]
11r	*p*-$MePhSO_3H$	0	—	—
11l	$MeSO_3H$	>95[e]	90:10	61[f]
11q	$MeSO_3H$	>95[e]	75:25	—[c]

[a]Nitro-Mannich: **10** (3 mmol), superhydride® (1.05 equiv. 1M in THF), CH_2Cl_2, rt, 1h; **11** (1.5 equiv.), Acid (2.6 equiv.), CH_2Cl_2, -78 °C, 1h then rt 1h. [b]Diastereoselectivities were calculated by comparison of the ^{1}H NMR signals for the CH_2CHNO_2 protons (~δ 3.1-3.6 ppm) of the crude reaction mixture. [c]Reaction not purified. [d]Isolated yield of pure *anti*-diastereoisomer. [e]$MeSO_3H$ (1.6 equiv.). [f]Isolated as a 90:10 mixture of diastereoisomers.

The desired intramolecular *N*-arylation reaction required the nitro group to be reduced with zinc dust and hydrochloric acid in ethanol. The crude *anti*-1,2-diamine **8** was treated directly with X-Phos and palladium acetate to provide diastereomerically pure 1,2,3,4-tetrahydroquinoxalines **7** in excellent yield (Scheme 4, Table 3). The X-phos ligand was required instead of the standard *N*-arylation conditions we have used previously[7a,b] because of the lower reactivity of the chloride substituent in *N*-arylation reactions.[11]

Scheme 4. Synthesis of 1,2,3,4-tetrahydroquinoxalines 7

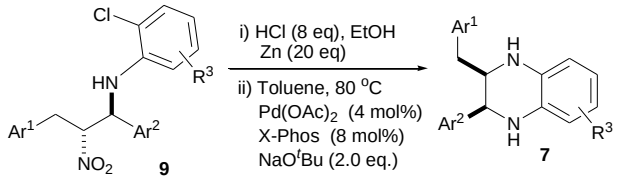


Table 3. Diversity of 1,2,3,4-tetrahydroquinoxalines 7[a]

Product	Ar^1	Ar^2	R^3	Yield (%)[b]
7b	Ph	Ph	H	80
7c	4-Me-Ph	Ph	H	74
7d	2-Me-Ph	Ph	H	70
7e	4-MeO-Ph	Ph	H	77
7f	2-MeO-Ph	Ph	H	68
7h	Ph	Ph	4-^{t}Bu	76
7i	Ph	Ph	4-F	63
7j	Ph	Ph	4-OMe	73
7l	Ph	Ph	5-CF_3	73[c]
7m	Ph	Ph	3-py	61
7n	Ph	3-MeO-Ph	H	69
7o	Ph	3-CF_3-Ph	H	71
7r	Ph	3-py	H	69

[a]Reduction: **9** (3 mmol), Zn (8 equiv) HCL (6M, 20 equiv) in EtOH (50 ml) at rt for 1 h. Cyclisation: Crude diamine **8** (3 mmol 1.0 eq.), NaO^{t}Bu (2 eq.), X-Phos (0.040 mmol, 8 mol%) and $Pd(OAc)_2$ (4 mol %) in PhMe (2.5 mL) at 90 °C for 3-12 hrs until complete conversion. [b]Isolated yield of diastereomerically pure product over two steps. [c]Isolated as a 90:10 mixture of diastereoisomers

Notably β-nitroamines **9g** and **9q** decomposed during the palladium catalysed *N*-arylation cyclisation step. Also 1,2,3,4-tetrahydroquinoxaline **7l** was isolated as an inseparable 90:10 mixture. Presumably some minor epimerisation occurred during the reduction step.

Extension of this methodology by using a carbon nucleophile in the initial conjugate addition nitro-Mannich reaction was investigated using $Et_2Zn/Cu(OTf)_2$ cat.[5a] and Grignard reagents. Variable diastereoselection, poor diastereoselctivity (60:40 to

80:20) and yields below 40% were observed. These results suggest that the 2-chloroaniline imine substituent is not suited to that particular reaction.

Conclusions

We have devised a synthetic strategy for the preparation of highly substituted 1,2,3,4-tetrahydroquinoxalines which uses the reductive conjugate addition nitro-Mannich reaction as a key stereochemical determining reaction in excellent yields and distereoselectivities. Subsequent nitro reduction followed by Pd-catalyzed intramolecular *N*-arylation completes the reactions sequence. Non basic imines were found to participate better in the nitro-Mannich reaction if the stronger acid methanesulfonic acid was used to promote the reaction instead of trifluoroacetic acid. This may enable other more difficult nitro-Mannich reactions to proceed. The reaction sequence is ideally suited to array synthesis as it allows the use of a wide range of aromatic aldehydes in the nitroalkene and imine reaction partners, with 2-chloro anilines.

Experimental

General Methods – please see ESI

General Procedure for the Synthesis of anti-β-Nitroamines 9 (Table 1)

A solution of superhydride® (3.15 mmol, 1 M in THF) was added to a solution of nitroalkene **10** (3 mmol) in CH_2Cl_2 (15 mL) under N_2 at rt and stirred for 1 h. The white suspension was then cooled to -78 ^oC, a solution of imine **11** (4.5 mmol) in CH_2Cl_2 (5 mL) was added and stirred for 5 min. Then a solution of TFA (4.8 mmol) in CH_2Cl_2 (1 mL) was then added dropwise, and the reaction stirred at -78 ^oC for 1 h, removed from the cold bath, stirred for a further 1 h at RT, and then quenched with saturated aq. $NaHCO_3$ (15 mL). The layers were separated, the aqueous phase further extracted with CH_2Cl_2 (2 x 20 mL), the combined organics washed with brine (10 mL), dried ($MgSO_4$), and the solvent removed in vacuo to give crude β-nitroamine. Diastereoselectivities were calculated by comparison of the 1H NMR signals for the CH_2CHNO_2 protons (δ 3.1-3.6 ppm). The crude β-nitroamine was then purified by column chromatography to yield diastereomerically pure, *anti*-β-nitroamine **9**.

(2*R, 3*S**)-2-Bromo-*N*-(2-nitro-1,3-diphenylpropyl)aniline** (**9a**)

Colourless oil; ^{1}H NMR (600 MHz; $CDCl_3$) δ 3.21 (1H, dd, *J* =14.9, 3.3, CH_{2a}), 3.46 (1H, dd, *J* =14.9, 10.5, CH_{2b}), 4.78 (1H, m, C*H*NH), 5.03 (1H, ddd, *J* =10.3, 5.2, 3.5, C*H*NO_2), 5.32 (1H, d, *J* =6.9, N*H*), 6.42 (1H, app. d, *J* =8.2, Ar*H*), 6.60 (1H, app. t, *J* =7.6, Ar*H*), 7.02 (1H, app. d, *J* =7.8, Ar*H*), 7.11-7.14 (2H, m, Ar*H*), 7.22-7.26 (1H, m, Ar*H*), 7.27-7.30 (2H, m, Ar*H*), 7.32-7.41 (5H, m, Ar*H*), 7.43-7.46 (1H, m, Ar*H*); ^{13}C NMR (151 MHz; $CDCl_3$) δ 34.9, 60.5, 93.4, 110.9, 112.9, 119.5, 127.0, 127.6, 128.5, 128.9, 129.0, 129.1, 129.4, 132.7, 135.4, 136.7, 142.8; IR (neat) 3392, 3030, 2916, 1595, 1550 cm^{-1}; Mass Spec (ES, M + H) Theoretical: 410.0624, Measured: 410.0634.

(2*R, 3*S**)-2-chloro-N-(2-nitro-1,3-diphenylpropyl)aniline** (**9b**)

White solid, mp 118-120 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.22 (1H, dd, *J*=14.8, 3.5), 3.46 (1H, dd, *J*=14.8, 10.3), 5.05 (1H, dd, *J*=7.0, 5.5), 5.13 (1H, ddd, *J*=10.0, 5.5, 3.5), 5.28 (1H, d, *J*=7.0), 6.46 (1H, dd, *J*=8.2, 1.1), 6.66 (1H, td, *J*=7.7, 1.5), 6.97 - 7.03 (1H, m), 7.12 (2H, d, *J*=6.5), 7.22-7.42 (9H, m); ^{13}C NMR (101 MHz; $CDCl_3$) δ 34.9, 60.3, 93.4, 112.8, 118.9, 120.3, 127.0, 127.5, 127.7, 128.8, 128.8, 128.9, 129.2, 129.3, 135.4, 136.8, 141.9; IR (neat) 3392, 3030, 2916, 1595, 1550 cm^{-1}; Mass Spec (ES, M + H) Theoretical: 367.1213, Measured: 367.1214.

(2*R, 3*S**)-2-chloro-N-(3-(4-methylphenyl)-2-nitro-1-phenylpropyl)aniline** (**9c**)

White solid, mp 98-100 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.31 (3H, s), 3.19 (1H, dd, *J*=14.8, 3.5), 3.42 (1H, dd, *J*=14.8, 10.3), 5.03 (1H, dd, *J*=7.0, 5.8), 5.09-5.16 (1H, m), 5.30 (1H, d, *J*= 7.0), 6.47 (1H, dd, *J*=8.2, 1.1), 6.66 (1H, td, *J*=7.7, 1.3), 6.95-7.05 (3H, m), 7.05-7.14 (2H, m), 7.25-7.42 (6H, m); ^{13}C NMR (101 MHz; $CDCl_3$) δ 21.0, 34.6, 60.2, 93.4, 112.7, 118.8, 120.2, 126.9, 127.7, 128.6, 128.8, 129.2, 129.3, 129.6, 132.2, 136.8, 137.1, 141.1; IR (neat) 3442, 3029, 2922, 1597, 1552 cm^{-1}; Mass Spec (ES, M + H) Theoretical: 381.1370 Measured: 381.1370.

(2*R, 3*S**)-2-chloro-N-(3-(2-methylphenyl)-2-nitro-1-phenylpropyl)aniline** (**9d**)

White solid, mp 117-118 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.11 (3H, s), 3.32 (1H, dd, *J*=15.2, 2.6), 3.53 (1H, dd, *J*=15.2, 10.4), 5.03-5.19 (2H, m), 5.32 (1H, d, *J*= 6.3), 6.45-6.57 (1H, m), 6.72 (1H, td, *J*=7.7, 1.3), 6.99-7.08 (1H, m), 7.08-7.22 (4H, m), 7.30-7.52 (6H, m); ^{13}C NMR (101 MHz; $CDCl_3$) δ 18.9, 31.8, 60.7, 92.5, 112.8, 118.9, 120.3, 126.5, 126.9, 127.6, 127.7, 128.8, 129.2, 129.3, 129.3, 129.4, 133.6, 136.1, 136.9,

141.9; IR (neat) 3403, 3064, 2925, 1596, 1552 cm^{-1}; Mass Spec (ES, M + H) Theoretical: 381.1370 Measured: 381.1366.

(2*R, 3*S**)-2-chloro-N-(3-(4-methoxyphenyl)-2-nitro-1-phenylpropyl)aniline** (**9e**)

White solid, mp 73-75 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.18 (1H, dd, *J*=14.8, 3.5), 3.41 (1H, dd, *J*=14.8, 10.3), 3.78 (3H, s), 4.96-5.06 (1H, m), 5.06-5.14 (1H, m), 5.28 (1H, d, *J*= 7.0), 6.47 (1H, dd, *J*=8.3, 1.0), 6.67 (1H, td, *J*=7.7, 1.3), 6.78-6.89 (2H, m), 6.95-7.10 (3H, m), 7.23-7.45 (6H, m); ^{13}C NMR (101 MHz; $CDCl_3$) δ 34.2, 55.3, 60.2, 93.6, 112.8, 114.4, 118.8, 120.2, 126.9, 127.2, 127.7, 128.8, 129.2, 129.3, 129.9, 136.8, 141.9, 159.0; IR (neat) 3402, 3032, 2933, 1596, 1551 cm^{-1}; Mass Spec (ES, M + H) Theoretical: 397.1319 Measured: 397.1314.

(2*R, 3*S**)-2-chloro-N-(3-(2-methoxyphenyl)-2-nitro-1-phenylpropyl)aniline** (**9f**)

White solid, mp 90-92 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.28 (1H, dd, *J*=14.4, 9.9), 3.45 (1H, dd, *J*=14.4, 3.1), 3.75 (3H, s), 5.02 (1H, app t, *J*=6.5), 5.21 (1H, ddd, *J*=9.9, 6.1, 3.2), 5.35 (1H, d, *J*=6.8), 6.47 (1H, dd, *J*=8.0, 1.0), 6.65 (1H, td, *J*=7.7, 1.5), 6.79-6.90 (2H, m), 6.94-7.03 (1H, m), 7.10 (1H, dd, *J*=7.7, 1.5), 7.18-7.43 (7H, m); ^{13}C NMR (101 MHz; $CDCl_3$) δ 31.0, 55.2, 60.4, 91.6, 110.4, 112.6, 118.5, 120.0, 120.8, 123.7, 127.0, 127.7, 128.6, 128.9, 129.0, 129.2, 131.0, 137.0, 142.0, 157.2; IR (neat) 3403, 3031, 2939, 1596, 1550 cm^{-1}; Mass Spec (ES, M + H) Theoretical: 397.1319 Measured: 397.1316.

(2*R, 3*S**)-2-chloro-N-(2-nitro-1-phenyl-3-(pyridin-3-yl)propyl)aniline** (**9g**)

Yellow oil; ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.23 (1H, dd, *J*=15.1, 2.5), 3.47 (1H, dd, *J*=15.1, 10.2), 5.02-5.16 (2H, m), 5.22 (1H, d, *J*=6.8), 6.50 (1H, dd, *J*=8.3, 1.3), 6.68 (1H, td, *J*=7.7, 1.5), 6.94 - 7.08 (1H, m), 7.20 (1H, dd, *J*=7.6, 4.8), 7.28 (1H, dd, *J*=7.9, 1.4), 7.31 - 7.47 (6H, m), 8.40 (1H, d, *J*=2.0), 8.50 (1H, dd, *J*=4.8, 1.5); ^{13}C NMR (101 MHz; $CDCl_3$) δ 32.3, 60.4, 92.9, 112.8, 119.1, 120.4, 123.8, 126.8, 127.8, 129.0, 129.4, 129.4, 131.5, 136.5, 136.9, 141.7, 148.4, 149.7; IR (neat) 3400, 3031, 1596, 1552 cm^{-1}; Mass Spec (ES, M + H) Theoretical: 367.1166 Measured: 367.1165.

(2*R, 3*S**)-4-(tert-butyl)-2-chloro-N-(2-nitro-1,3-diphenylpropyl)aniline** (**9h**)

White solid, mp 125-127 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.24 (9H, s, Bu^{t}), 3.24 (1H, dd, *J*=14.9, 3.4), 3.47 (1H, dd, *J*=14.8, 10.5), 5.03 (1H, dd, *J*=6.8, 5.8), 5.08-5.18 (2H, m,), 6.44 (1H, d, *J*=8.5), 7.03 (1H, dd, *J*=8.5 and 2.3), 7.08-7.16 (2H, m), 7.22-7.41 (9H,

m); ^{13}C NMR (101 MHz; CDCl3) δ 31.3, 34.0, 35.0, 60.6, 93.6, 112.5, 120.0, 124.6, 126.4, 126.9, 127.5, 128.8, 128.9, 129.2, 135.5, 137.1, 139.5, 142.2; IR (neat) 3404, 3032, 2962, 1611, 1551 cm^{-1}; Mass Spec (ES, M + H) Theoretical: 423.1839 Measured: 423.1833.

(2*R, 3*S**)-2-chloro-4-fluoro-N-(2-nitro-1,3-diphenylpropyl)aniline** (**9i**)

White solid, mp 109-112 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.21 (1H, dd, *J*=14.9, 3.6), 3.46 (1H, dd, *J*=14.9, 10.4), 4.99 (1H, dd, *J*=6.8, 5.5), 5.09-5.20 (2H, m), 6.37 (1H, dd, *J*=6.8, 5.5), 6.73 (1H, td, *J*=8.5, 2.9), 7.01 (1H, dd, *J*=8.5 and 2.3), 7.09-7.16 (2H, m), 7.21-7.44 (8H, m); ^{13}C NMR (101 MHz; $CDCl_3$) δ 34.8, 60.8, 93.2, 113.2 (d, J_{CF}=8.0), 114.4 (d, J_{CF}=22.4), 116.7 (d, J_{CF}=25.6), 120.3 (d, J_{CF}=10.4), 126.8, 127.5, 128.8, 128.9, 129.3, 135.3, 136.5, 138.6 (d, J_{CF}=3.2), 155.2 (d, J_{CF}=240.5); ^{19}F NMR (376 MHz, $CDCl_3$) ppm -63.11 (s); IR (neat) 3405, 3031, 1552, 1509 cm^{-1}; Mass Spec (ES, M + H) Theoretical: 385.1119 Measured: 385.1119.

(2*R, 3*S**)-2-chloro-4-methoxy-N-(2-nitro-1,3-diphenylpropyl)aniline** (**9j**)

White solid, mp 125-127 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.23 (1H, dd, *J*=14.8, 3.5), 3.46 (1H, dd, *J*=14.8, 10.3), 3.64 (3H, s), 5.01 (1H, dd, *J*=7.0, 5.8), 5.14 (1H, ddd, *J*=10.2, 5.7, 3.5), 5.27 (1H, d, *J*=7.0),6.04 (1H, d, *J*=2.8), 6.23 (1H, dd, *J*=8.5, 2.8), 7.13 (2H, d, *J*=6.8), 7.17 (1H, d, *J*=8.5), 7.23-7.32 (3H, m), 7.33-7.43 (5H, m); ^{13}C NMR (101 MHz; CDCl3) δ 34.9, 55.3, 60.3, 93.3, 99.8, 103.4, 112.2, 126.8, 127.5, 128.8, 128.9, 128.9, 129.3, 129.5, 129.3, 135.3, 136.6, 142.6, 159.4; IR (neat) 3402, 3031, 2937, 1602, 1553 cm^{-1}; Mass Spec (ES, M + H) Theoretical: 397.1319 Measured: 397.1330.

(2*R, 3*S**)-2-chloro-N-(2-nitro-1,3-diphenylpropyl)-5-(trifluoromethyl)aniline** (**9l**)

Oil; ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.18 (1H, dd, *J*=14.8, 4.0), 3.43 (1H, dd, *J*=14.8, 10.3), 5.02 (1H, dd, *J*=6.9, 5.4), 5.15 (1H, ddd, *J*=10.3, 5.1, 3.8), 5.52 (1H, d, *J*=7.0), 6.59-6.64 (1H, m), 6.90 (1H, dd, *J*=8.3, 1.3), 7.08-7.16 (2H, m), 7.19 - 7.45 (9H, m); ^{13}C NMR (101 MHz; $CDCl_3$) δ 34.5, 59.7, 92.4, 108.7 (*Ar*, *J*=4.0), 115.0 (*Ar*, *J*=4.0), 123.2 (q, *J*=1.6), 123.3 (q, *J*=272.4), 126.5, 127.3, 128.5, 128.7, 128.9, 129.1, 129.3, 129.9 (q, *J*=32.8), 134.7, 135.3, 141.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.4; IR (neat) 3402, 3066, 3032, 1604, 1552 cm^{-1}; Mass Spec (ES, M + H) Theoretical: 435.1087 Measured: 435.1080.

(2*R, 3*S**)-2-chloro-N-(2-nitro-1,3-diphenylpropyl)pyridin-3-amine** (**9m**)

White solid, mp 142-144 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.18 (1H, dd, *J*=14.8, 3.8), 3.45 (1H, dd, *J*=14.8, 10.3), 4.93-5.04 (1H, m), 5.16 (1H, ddd, *J*=10.3, 5.1, 3.8), 5.41 (1H, d, *J*=6.8), 6.65 (1H, dd, *J*=8.0, 1.3), 6.94 (1H, dd, *J*=8.0, 4.8), 7.11 (2H, d, *J*=6.5), 7.19 - 7.45 (8H, m), 7.74 (1H, dd, *J*=4.5, 1.5); ^{13}C NMR (101 MHz; $CDCl_3$) δ 34.7, 59.9, 92.9, 119.2, 123.2, 126.8, 126.8, 127.6, 128.8, 129.1, 129.4, 135.0, 135.7, 138.0, 138.7; IR (neat) 3401, 3032, 1583, 1551 cm^{-1}; Mass Spec (ES, M + H) Theoretical: 367.1166 Measured: 367.1158.

(2*R, 3*S**)-2-chloro-N-(1-(3-methoxyphenyl)-2-nitro-3-phenylpropyl)aniline** (**9n**)

White solid, mp 88-90 °C; ^{1}H NMR (400 MHz; CDCl3) δ 3.20 (1H, dd, *J*=14.8, 3.5), 3.44 (1H, dd, *J*=14.8, 10.5), 3.78 (3H, s), 4.95-5.04 (1H, m), 5.07-5.15 (1H, m), 5.24 (1H, d, *J*=7.0), 6.45 (1H, dd, *J*=8.3, 1.3), 6.66 (1H, td, *J*=7.7, 1.3), 6.83-6.90 (2H, m), 6.93-7.03 (2H, m), 7.07-7.13 (2H, m), 7.22-7.32 (5H, m); ^{13}C NMR (101 MHz; CDCl3) δ 34.8, 55.3, 60.3, 93.3, 112.8, 112.8, 113.9, 118.9, 119.0, 120.3, 127.5, 127.7, 128.8, 128.9, 129.3, 130.3, 135.4, 138.5, 141.9, 160.2; IR (neat) 3404, 3030, 2936, 1596, 1551 cm^{-1}; Mass Spec (ES, M + H) Theoretical: 397.1319 Measured: 397.1330.

(2*R, 3*S**)-2-chloro-N-(2-nitro-3-phenyl-1-(3-(trifluoromethyl)phenyl)propyl)aniline** (**9o**)

Colourless oil; ^{1}H NMR (400 MHz; $CDCl_3$) for major isomer δ 3.26 (1H, dd, *J*=14.8, 3.8,), 3.51 (1H, dd, *J*=14.8, 10.0), 5.09-5.15 (1H, m), 5.21 (1H, ddd, *J*=10.0, 5.8, 3.8), 5.35 (1H, d, *J*=7.03), 6.46 (1H, dd, *J*=8.2, 1.1), 6.74 (1H, td, *J*=7.7, 1.4), 7.03 - 7.09 (1H, m), 7.14-7.20 (2H, m), 7.26-7.38 (4H, m), 7.49 - 7.71 (4H, m); ^{13}C NMR for major isomer δ (101 MHz; $CDCl_3$) 35.1, 59.9, 92.8, 112.7, 119.3, 120.4, 131.6 (q, *J*=272.2 Hz), 123.8 (q, *J*=3.7), 125.8 (q, *J*=3.5), 127.7, 127.8, 128.8, 129.0, 129.5, 129.8, 130.2, 131.6 (q, *J*=32.5 Hz), 134.8, 138.1, 141.4; IR (neat) 3403, 3032, 2926, 1596, 1554 cm^{-1}; Mass Spec (ES, M + H) Theoretical: 435.1087 Measured: 435.1094.

(2*R, 3*S**)-2-chloro-N-(2-nitro-3-phenyl-1-(pyridin-3-yl)propyl)aniline** (**9q**)

Yellow oil; ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.27 (1H, dd, *J*=14.6, 4.0, CH_a), 3.46 (1H, dd, *J*=14.6, 9.0, CH_b), 4.90-5.08 (3H, m, *J*=9.5, 5.8, C*H*NH, C*H*NO_2 and N*H*), 6.37 (1H, d, *J*=1.0, Ar*H*), 6.57 (1H, d, *J*=8.2, Ar*H*), 6.70 (1H, dt, *J*=7.7, 1.3, Ar*H*), 7.03-7.11 (1H, m, Ar*H*), 7.13-7.20 (2H, m, Ar*H*), 7.23-7.35 (4H, m, Ar*H*), 7.39-7.45 (2H, m, Ar*H*); ^{13}C NMR (101 MHz; $CDCl_3$) δ 35.7, 52.7, 92.2, 108.3, 112.6, 119.2, 120.3, 121.9, 127.6, 127.8,

128.9, 129.0, 129.5, 135.2, 140.7, 141.8, 144.3; IR (neat) 3405, 3030, 2936, 1597, 1554 cm^{-1}; Mass Spec (ES, M + H) Theoretical: 357.1006 Measured: 357.0997.

(2*R, 3*S**)-2-chloro-N-(2-nitro-3-phenyl-1-(pyridin-3-yl)propyl)aniline** (**9r**)

White solid, mp 101-103 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.26 (1H, dd, *J*=14.8, 4.0), 3.45 (1H, dd, *J*=14.8, 9.8), 4.99-5.08 (1H, m), 5.13-5.23 (1H, m), 5.29 (1H, d, *J*=8.0), 6.44 (1H, d, *J*=8.0), 6.64-6.75 (1H, m), 6.94-7.07 (1H, m), 7.16 (2H, d, *J*=6.5), 7.27 - 7.35 (5H, m), 7.62 - 7.70 (1H, m), 8.61 (1H, dd, *J*=4.8, 1.5), 8.68 (1H, d, *J*=2.3); ^{13}C NMR (101 MHz; $CDCl_3$) δ 35.5, 58.0, 92.7, 112.7, 119.4, 120.4, 124.0, 127.7, 127.8, 128.8, 129.0, 129.5, 132.4, 134.3, 134.7, 141.2, 148.9, 150.3; IR (neat) 3400, 3033, 1595, 1553 cm^{-1}; Mass Spec (ES, M + H) Theoretical: 367.1166 Measured: 367.1171.

General Procedure for the Synthesis of 1,2,3,4-tetrahydroquinoxalines 7 (Table 3)

To a solution of β-nitroamine **9** (3.0 mmol 1.0 eq.) in EtOH (50 mL) was added Zinc (24.0 mmol, 8 equiv) follow by hydrochloric acid (60.0 mmol, 6M, 20 eq.). The reaction mixture was stirred at rt for 1 h and the solvent removed in vacuo. A saturated aq. solution of $NaHCO_3$ (20 mL) was added and the mixture was extracted with EtOAc (3 x 20 mL), the combined organics washed with brine (10 mL), dried ($MgSO_4$) and the solvent removed in vacuo to give crude 1,2-diamine **8**.

A solution of the crude 1,2-diamine **8** in PhMe (1.5 mL) was added to ^{t}BuONa (1.00 mmol, 2.0 equiv), X-Phos (0.040 mmol, 8 mol%) and palladium(II) acetate (0.020 mmol, 4 mol%) in PhMe (1mL) under N_2 at rt. The reaction was heated to 90 °C for 3-12 hrs until complete conversion. The reaction mixture was allowed to cool to rt, filtered thought celite and concentrated to give crude 1,2,3,4-tetrahydroquinoxaline **7** which was purified by column chromatography.

(2*R, 3*S**)-2-benzyl-3-phenyl-1,2,3,4-tetrahydroquinoxaline** (**7b**)

Yellow solid, mp 63-65 °C; ^{1}H NMR (600 MHz; $CDCl_3$) δ 2.47 (1H, dd, *J* =13.5, 10.7), 2.57 (1H, dd, *J* =13.5, 3.3), 3.70 (1H, s), 3.73 (1H, app. dt, *J* =10.7, 3.3), 4.00 (1H, s), 4.76 (1H, d, *J* =2.9), 6.47 (1H, dd, *J* =7.6, 1.3), 6.59 (1H, dd, *J* =7.5, 1.4), 6.63 (1H, td, *J* =7.5, 1.4), 6.67 (1H, td, *J* =7.4, 1.3), 7.02-7.06 (2H, m), 7.19-7.23 (1H, m), 7.25-7.29 (2H, m), 7.31-7.34 (1H, m), 7.36-7.43 (4H, m); ^{13}C NMR (151 MHz; $CDCl_3$) δ 36.5, 55.7, 58.1, 114.3, 115.0, 118.9, 119.2, 126.5, 127.6, 127.7, 128.6, 128.7, 128.5, 132.1,

133.4, 138.8, 141.6; IR (neat) 3384, 3060, 3025, 1550, 1504 cm^{-1}; Mass Spec (EI) Theoretical: 300.1621 Measured: 300.1627.

(2*R, 3*S**)-2-(4-methylbenzyl)-3-phenyl-1,2,3,4-tetrahydroquinoxaline** (**7c**)

Yellow solid, mp 63-65 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.36 (3H, s), 2.47 (1H, dd, *J* =13.3, 10.5), 2.57 (1H, dd, *J* =13.3, 3.5), 3.75 (1H, app. dt, *J* =10.4, 3.5), 3.93 (2H, br. s), 4.77 (1H, d, *J* =3.0), 6.50 (1H, d, *J* =7.3, 1.5), 6.57-6.76 (3H, m), 6.93-7.01 (2H, m), 7.06-7.17 (2H, m), 7.30-7.48 (5H, m); ^{13}C NMR (101 MHz; $CDCl_3$) δ 21.0, 36.0, 55.6, 58.0, 114.2, 114.8, 118.7, 119.1, 127.5, 127.5, 128.4, 129.2, 129.3, 132.1, 133.3, 135.5, 135.9, 141.7; IR (neat) 3376, 3023, 2920, 1508 cm^{-1}; Mass Spec (ES, M + H) Theoretical: 315.1861 Measured: 315.1855.

(2*R, 3*S**)-2-(2-methylbenzyl)-3-phenyl-1,2,3,4-tetrahydroquinoxaline** (**7d**)

Yellow solid, mp 58-60 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.00 (3H, s), 2.53 (1H, dd, *J* =13.7, 10.3), 2.61 (1H, dd, *J* =13.7, 3.3), 3.69 (1H, app. dt, *J* =10.4, 3.1), 3.89 (2H, br. s), 4.83 (1H, d, *J* =3.0), 6.50 (1H, d, *J* =7.0, 1.8), 6.59-6.71 (3H, m), 6.93-7.01 (1H, m), 7.09-7.15 (3H, m), 7.33-7.50 (5H, m); ^{13}C NMR (101 MHz; $CDCl_3$) δ 18.7, 32.7, 54.2, 57.7, 114.1, 114.6, 118.7, 125.6, 126.2, 127.0, 127.3, 128.1, 129.8, 130.2, 131.8, 132.9, 136.4, 136.7, 141.1; IR (neat) 3368, 3022, 2925, 1505 cm^{-1}; Mass Spec (ES, M + H) Theoretical: 315.1861 Measured: 315.1854.

(2*R, 3*S**)-2-(4-methoxybenzyl)-3-phenyl-1,2,3,4-tetrahydroquinoxaline** (**7e**)

Yellow solid, mp 58-60 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.45 (1H, dd, *J* =13.7, 10.7), 2.55 (1H, dd, *J* =13.7, 3.6), 3.73 (1H, app. dt, *J* =10.5, 3.4), 3.82 (3H, s), 3.86 (2H, br. s), 4.76 (1H, d, *J* =3.0), 6.51 (1H, d, *J* =7.4, 1.6), 6.59-6.75 (3H, m), 6.80-6.90 (2H, m), 6.95-7.03 (2H, m), 7.32-7.45 (5H, m); ^{13}C NMR (101 MHz; $CDCl_3$) δ 35.5, 55.2, 55.6, 57.9, 114.0, 114.2, 115.0, 118.7, 119.3, 127.5, 127.6, 128.4, 130.3, 130.4, 131.8, 133.3, 141.5, 158.3; IR (neat) 3373, 3027, 2950, 1510 cm^{-1}; Mass Spec (ES, M + H) Theoretical: 331.1810 Measured: 331.1807.

(2*R, 3*S**)-2-(2-methoxybenzyl)-3-phenyl-1,2,3,4-tetrahydroquinoxaline** (**7f**)

Yellow solid, mp 55-57 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.43 (1H, dd, *J* =13.3, 10.3), 2.78 (1H, dd, *J* =13.3, 3.0), 3.76 (3H, s), 3.82 (2H, br. s), 3.91 (1H, app. dt, *J* =10.1, 3.0), 4.80 (1H, d, *J* =3.0), 6.54 (1H, d, *J* =7.3, 1.5), 6.61-6.77 (3H, m), 6.84-6.97 (2H, m), 7.02 (1H, dd, *J* =7.3, 1.5), 7.22-7.31 (1H, m), 7.35-7.55 (5H, m); ^{13}C NMR (101

MHz; $CDCl_3$) δ 32.0, 53.5, 55.1, 58.1, 110.4, 114.1, 114.8, 118.5, 118.9, 120.4, 127.1, 127.3, 127.5, 127.8, 128.2, 131.2, 132.5, 133.2, 141.8, 157.8; IR (neat) 3374, 3027, 2949, 1510 cm^{-1}; Mass Spec (ES, M + H) Theoretical: 331.1810 Measured: 331.1802.

(2*R, 3*S**)-3-benzyl-6-tert-butyl-2-phenyl-1,2,3,4-tetrahydroquinoxaline** (**7h**)

Yellow solid, mp 64-65 °C; ^1H NMR (400 MHz; $CDCl_3$) δ 1.30 (9H, s), 2.50 (1H, dd, *J* =13.6, 10.5), 2.59 (1H, dd, *J* =13.6, 3.5), 3.76 (1H, app. dt, *J* =10.5, 3.3), 3.78 (2H, br s), 4.74 (1H, d, *J* =3.0), 6.48-6.58 (2H, m), 6.71 (1H, dd, *J* =8.3, 2.0), 7.06 (2H, d, *J* =7.0), 7.02-7.44 (8H, m); ^{13}C NMR (101 MHz; $CDCl_3$) δ 31.6, 33.9, 36.5, 55.8, 58.2, 112.3, 113.8, 115.9, 126.3, 127.5, 127.5, 128.4, 128.5, 129.4, 130.8, 131.5, 138.8, 141.8, 141.9; IR (neat) 3379, 3026, 2959, 1521 cm^{-1}; Mass Spec (ES, M + H) Theoretical: 357.2331 Measured: 357.2318.

(2*R, 3*S**)-3-benzyl-6-fluoro-2-phenyl-1,2,3,4-tetrahydroquinoxaline** (**7i**)

Yellow solid, mp 53-55 °C; ^1H NMR (400 MHz; $CDCl_3$) δ 2.50-2.64 (2H, m), 3.75 (1H, td, *J* =9.8, 3.8), 3.84 (2H, br s), 4.75 (1H, d, *J* =3.0), 6.23 (1H, dd, *J* =10.0, 2.5), 6.39 (1H, td, *J* =8.5, 2.8), 6.52 (1H, dd, *J* =8.5, 5.3), 7.07 (2H, d, *J* =7.0), 7.20-7.50 (8H, m); ^{13}C NMR (101 MHz; $CDCl_3$) δ 36.2, 55.8, 57.8, 101.5 (d, J_{CF}=26.4), 104.5 (d, J_{CF}=22.4), 114.5 (d, J_{CF}=8.8), 126.5, 127.3, 127.7, 128.5, 128.6, 129.1, 129.4, 133.0 (d, J_{CF}=10.4), 138.6, 141.2, 156.9 (d, J_{CF}=234.1); ^{19}F NMR (376 MHz, $CDCl_3$) δ -125.9 (s); IR (neat) 3379, 3026, 2959, 1521 cm^{-1}; Mass Spec (ES, M + H) Theoretical: 319.1611 Measured: 319.1602.

(2*R, 3*S**)-3-benzyl-6-methoxy-2-phenyl-1,2,3,4-tetrahydroquinoxaline** (**7j**)

Yellow oil; ^1H NMR (400 MHz; $CDCl_3$) δ 2.47 (1H, dd, *J* =13.6, 10.5), 2.56 (1H, dd, *J* =13.6, 3.5), 3.67-3.75 (1H, m), 3.73 (3H, s), 4.74 (1H, d, *J* =3.0), 6.20-6.25 (2H, m), 6.44 (1H, d, *J* =9.0), 7.04 (2H, app. d, *J* =7.0), 7.19 - 7.41 (8H, m); ^{13}C NMR (101 MHz; $CDCl_3$) δ 36.1, 55.5, 55.8, 58.0, 100.7, 103.5, 116.1, 125.0, 126.4, 127.5 (2C), 127.6, 128.4 (2C), 128.6 (2C), 129.3 (2C), 134.6, 138.5, 141.3, 153.9; IR (neat) 3369, 3027, 2932, 1517 cm^{-1}; Mass Spec (ES, M + H) Theoretical: 331.1810 Measured: 331.1797.

(2*R, 3*S**)-2-benzyl-3-phenyl-6-(trifluoromethyl)-1,2,3,4-tetrahydroquinoxaline** (**7l**)

White solid, mp 50-53 °C; ^1H NMR (400 MHz; $CDCl_3$) δ 2.45 (1H, dd, *J* =13.4, 10.7), 2.57 (1H, dd, *J* =13.4, 3.5), 3.74 (1H, app dt, *J* =10.6, 3.4), 3.98 (2H, br s), 4.74 (1H, d, *J* =3.3), 6.43 (1H, d, *J* =8.3), 6.77-6.80 (1H, m), 6.86 (1H, d, *J* =8.0), 7.02 (2H, d, *J* =6.8),

7.21-7.30 (3H, m,), 7.30-7.40 (5H, m); ^{13}C NMR (101 MHz; $CDCl_3$) δ 36.5, 55.5, 57.6, 110.6 (q, *J*=4.0), 113.6, 116.0 (q, *J*=4.0), 120.6 (q, *J*=32.2), 124.9 (q, *J*=270.8),126.6, 127.4, 127.9, 128.6, 128.7, 129.3, 132.8, 134.9, 138.3, 140.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.7 (s); IR (neat) 3390, 3029, 2853, 1491 cm^{-1}; Mass Spec (ES, M + H) Theoretical: 369.1579 Measured: 369.1575.

(2*R, 3*S**)-3-benzyl-2-phenyl-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine** (**7m**)

Yellow solid, mp 58-61 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.43 (1H, dd, *J* =13.4, 10.7), 2.62 (1H, dd, *J* =13.4, 3.3), 3.87-3.94 (1H, m), 4.03 (1H,br s), 4.70 (1H, d, *J* =3.0), 4.81 (1H, s), 6.56 (1H, dd, *J* =7.5, 5.0), 6.74 (1H, d, *J* =6.8), 7.05 (2H, d, *J* =7.3), 7.19-7.43 (8H, m), 7.56 (1H, d, *J* =4.3); ^{13}C NMR (101 MHz; $CDCl_3$) δ 37.3, 55.5, 57.5, 114.4, 118.6, 126.6, 127.5, 127.9, 128.5, 128.6, 128.7, 129.3, 137.2, 137.9, 140.7, 145.9; IR (neat) 3388, 3321, 3027, 2923, 1493 cm^{-1}; Mass Spec (ES, M + H) Theoretical: 302.1657 Measured: 302.1646.

(2*R, 3*S**)-2-benzyl-3-(3-methoxyphenyl)-1,2,3,4-tetrahydroquinoxaline** (**7n**)

Yellow oil; ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.54 (1H, dd, *J* =13.3, 9.8), 2.60 (1H, dd, *J* =13.3, 4.3), 3.73 (1H, m), 3.83 (3H, s), 4.76 (1H, d, *J* =3.0), 6.48 (1H, dd, *J* =7.4, 1.6), 6.59-6.71 (3H, m), 6.89 (1H, dd, *J* =8.0, 2.3), 6.99 - 7.09 (4H, m), 7.21 - 7.35 (4H, m); ^{13}C NMR (101 MHz; $CDCl_3$) δ 36.2, 55.2, 55.8, 57.8, 112.7, 113.2, 114.3, 114.9, 118.9, 119.0, 119.7, 126.4, 128.6, 129.4, 129.5, 131.9, 133.2, 138.8, 143.2, 159.7; IR (neat) 3372, 3025, 2947, 1504 cm^{-1}; Mass Spec (ES, M + H) Theoretical: 331.1810 Measured: 331.1802.

(2*R, 3*S**)-2-benzyl-3-(3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroquinoxaline** (**7o**)

Yellow solid, mp 49-51 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.55 (2H, d, *J* =7.3), 3.87 (1H, td, *J* =7.3, 3.0), 4.74 (1H, d, *J* =3.0), 5.65 (2H, br s), 6.63 (1H, dd, *J* =7.3, 1.3), 6.67-6.75 (2H, m), 6.75-6.88 (1H, m), 7.00 (2H, d, *J* =6.8), 7.18-7.32 (3H, m), 7.40-7.55 (1H, m), 7.58-7.69 (3H, m); ^{13}C NMR (101 MHz; $CDCl_3$) δ 35.2, 55.4, 57.1, 115.6, 117.0, 120.0, 121.8, 124.0 (q, *J*=272.4), 124.3 (q, *J*=3.5), 124.9 (q, *J*=3.5), 127.0, 128.1, 128.6, 129.2, 129.3, 130.8 (q, *J*=32.8), 130.9, 132.9, 137.1, 141.0; ^{19}F NMR (376; $CDCl_3$) δ -63.0 (s); IR (neat) 3371, 3028, 1505 cm^{-1}; Mass Spec (ES, M + H) Theoretical: 369.1579 Measured: 369.1569.

(2*R, 3*S**)-2-benzyl-3-(pyridin-3-yl)-1,2,3,4-tetrahydroquinoxaline** (**7r**)

Yellow solid, mp 55-58 ^{o}C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.40 (1H, dd, *J* =13.6, 10.3), 2.60 (1H, dd, *J* =13.6, 4.0), 3.72 (1H, br s), 3.85 (1H, app dt, *J* =10.1, 3.6), 4.07 (1H, br s), 4.69 (1H, d, *J* =2.8), 6.41-6.54 (1H, m), 6.59 (1H, dd, *J* =7.3, 1.5), 6.63-6.74 (2H, m), 7.09 (2H, d, *J* =7.3), 7.24-7.36 (4H, m), 7.73 (1H, d, *J* =8.0), 8.55-8.64 (2H, m); ^{13}C NMR (101 MHz; $CDCl_3$) δ 37.3, 54.7, 56.0, 114.4, 114.9, 118.9, 119.5, 123.6, 126.7, 128.7, 129.2, 132.0, 132.5, 135.4, 137.2, 137.7, 149.0, 149.2; IR (neat) 3372, 3321, 3027, 2919, 1602, 1504 cm^{-1}; Mass Spec (ES, M + H) Theoretical: 302.1657 Measured: 302.1658.

Acknowledgements

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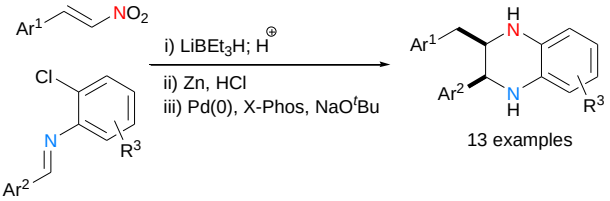
Table of contents graphic



A reductive conjugate addition nitro-Mannich reaction controls diastereoselectivity in a rapid entry to a diverse array of 1,2,3,4-tetrahydroquinoxalines in high yield.