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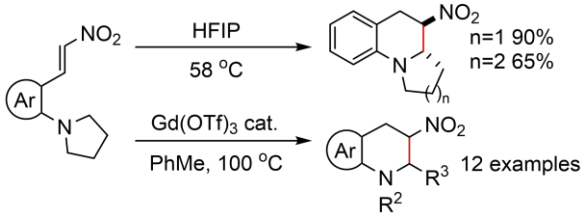

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Investigation of the [1,5]-hydride shift as a route to nitro-Mannich cyclisations

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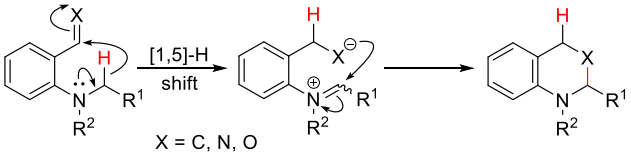
ABSTRACT

Conditions were found for the [1,5]-hydride shift nitro-Mannich reaction that led to the synthesis of 2,3-disubstituted tetrahydroquinolines. Two simple cyclic amine substrates gave diastereomerically pure rearranged products in 65 and 90% yields by refluxing in HFIP. A more general procedure used Gd(OTf)3 as a catalyst and successfully rearranged other cyclic and acyclic amines in 42-84% yield with diastereomeric ratios of 75:25 to >95:5 in favour of the anti-diastereoisomer (9 examples). Two examples of sulfur containing heterocycles gave lower yields of 9 and 25%. Electron withdrawing substituents were shown to have a deleterious effect on the success of the reaction. The results indicated the limitation of the [1,5]-hydride shift nitro-Mannich reaction with respect to the stability of the intermediate iminium ion.

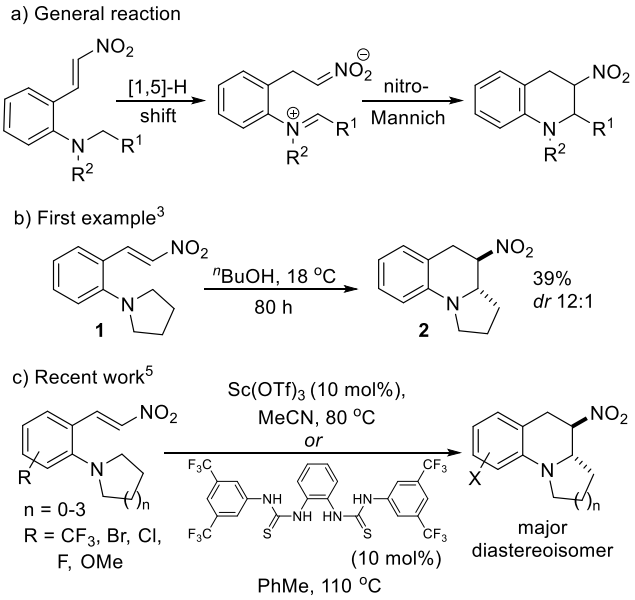
1. Introduction

The functionalisation of Csp3-H bonds adjacent to an amine via 1,5-hydride transfer and subsequent nucleophilic cyclisation represents a redox-neutral reaction cascade that has proven useful for the synthesis of structurally diverse amino heterocycles (for example Scheme 1).[1] Amongst the examples of hydride acceptors (C=X, Scheme 1), the use of carbonyls, imines, and especially α,β-unsaturated carbonyl and malonic acid derivatives are the most prevalent.[2]



Scheme 1. [1,5]-H shift cyclisation reaction

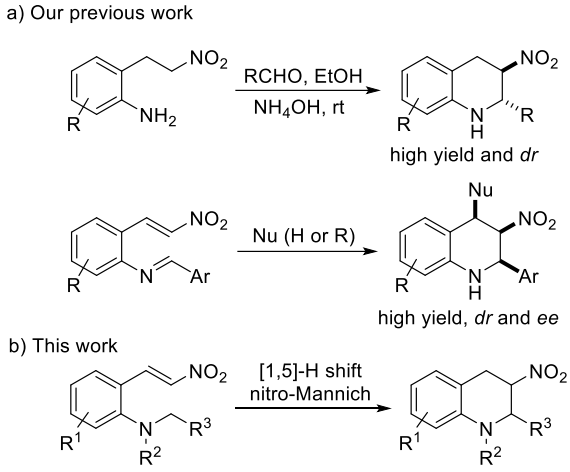
The use of the nitro alkene function as a hydride acceptor in these reactions would enable a nitro-Mannich cyclisation to occur (Scheme 2a), but reports of this are scarce. An isolated report detailing thermal conditions by Rabong et al. (Scheme 2b) indicated the probable difficulty of this process in comparison to the use of α,β-unsaturated carbonyl derivatives.[3] The addition of an ester stabilising group revealed that α-nitroacrylate esters were competent substrates for the [1,5]-H shift, but required the use of a catalytic Lewis acid ($Mg(OTf)_2$ 10 mol%) in addition to heat.[4] During our studies of this reaction Kim reported thermal Lewis acid catalysed and thiourea catalysed examples of cyclic amines (Scheme 2c).[5]



Scheme 2. The [1,5]-H shift nitro-Mannich reaction

We set out to investigate the use of nitro alkenes as hydride acceptors in these sorts of processes more fully as we recognised it could simplify our previous synthesis of 2,3-functionalised[6] and 2,3,4-functionalised[7] terahydroquinolines by a nitro-Mannich type cyclisation (Scheme 3). The nitro-Mannich reaction[8] is useful for the synthesis of stereodefined β-nitroamines that can be used in heterocycle synthesis.[9] Tetrahydroquinolines are an important motif in many biologically active natural products and medicinal compounds,[10] often requiring the *de novo* constructions of the heterocycle. A particularly efficient and versatile approach has

made use of the nitro-Mannich cyclisation of nitro nucleophiles onto a pendant aniline imine to give stereodefined nitro-substituted tetrahydroquinolines.[6,7,11] Our previous work relied upon the formation of an imine by condensation of an aniline with an aldehyde and then cyclisation with either a nitronic acid nucleophilic formed by a weak acid or nitronate anion formation from an intermolecular nucleophilic conjugate addition to a nitro styrene (Scheme 3a). We report here our studies into the scope and limitations of the [1,5]-H shift nitro-Mannich reaction for the synthesis of 2,3-disubstiuted tetrahydroquinolines that expands the use of anilines in this process (Scheme 3b). Our results compliment those of Rabong and Kim. We show that piperidines as well as pyrrolidines can be rearranged in high yields, that the rearrangement is very substrate dependent, but that certain acyclic benzylic and alkyl amines will rearrange. Our results expands the substrate scope of the rearrangement, definitively confirm the sense of diastereoselection and give some rationale to guide the use of this rearrangement in target synthesis.

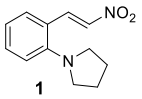
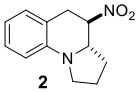
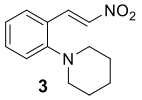
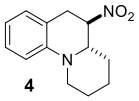
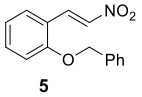
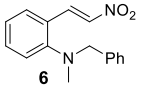


Scheme 3. Synthesis of isoquinolines by the nitro-Mannich reaction

2. Results and discussion

Repeat of the literature conditions to rearrange **1** (nBuOH, reflux, 80 h) gave only 5% of desired product **2** (Lit 39%, Scheme 2b).[3] The *anti*-stereochemistry was assigned from the 1H NMR with a key *trans* diaxial coupling of 9.7 Hz across the nitroamine,[3] which was later supported by the single crystal X-ray determination of a similar analogue (*vide infra*). Repeating the reaction in PhMe at reflux saw only degradation over 80 h. To investigate this reaction further we studied the effect of hydrogen bond activation on this process. We speculated that a more acidic solvent might lead to a higher yielding reaction due to enhanced hydrogen bonding to the nitro alkene. This would lead to a better hydride acceptor and faster reaction if we assumed hydride migration was the rate determining step. Refluxing **1** in CF_3CH_2OH was complete by tlc in 9.5 h and led to a 55% isolated yield of **2** (Table 1) as a single diastereoisomer. Use of the more acidic alcohol heaxafluoroisopropanol (HFIP) led to a 90% yield in 4 h. In retrospect HFIP is also known to stabilise cations due to its high dielectric constant and may also help lower the activation energy of the reaction by stabilising the developing iminium cation after hydride migration (Scheme 2a).[12] While preparing this manuscript reports appeared using the unique properties of HFIP to promote 1,5-hydride transfer from anilines to a quinone methides. We decided to explore the scope of the reaction with HFIP.[13] The use of HFIP in a stoichiometric amount in refluxing PhMe or CH_2Cl_2 led to recovered starting material. The piperidinyl analogue (*E*)-1-(2-(2-nitrovinyl)phenyl)piperidine (**3**)[2b,3] had only given unquantifiable traces of product in the original nBuOH method[3] and in the thiourea catalysed examples by Kim.[5a] Refluxing in HFIP for a longer time period of 18 h we were able to isolate the desired cyclised product **4** in 65%, as a single diastereoisomer. The coupling constant across the nitro amine is only 6.2 Hz, which is some way off the magnitude expected for a *trans*-diaxial coupling if we assumed the substituents occupied a *pseudo* equatorial conformation. The *anti*-stereochemistry is depicted by Kim[5] for this and related ring fused products, but no structural proof was published. We have tentatively assigned the *anti*-stereochemistry to **4** based on comparison of its 1H NMR data with other analogues (*vide infra*). As an aside we did attempt the use of Schreiner's thio-urea catalyst[14] (5 mol%) for the rearrangement of **3** in refluxing toluene for 4 days after no reaction at room temperature. Analysis by tlc revealed mainly starting material, with some other spots which did not correspond to the desired product **4**. This was in line with the observations of Kim who found that thio-urea catalysis or thermal conditions did not rearrange substrate 3.[5]

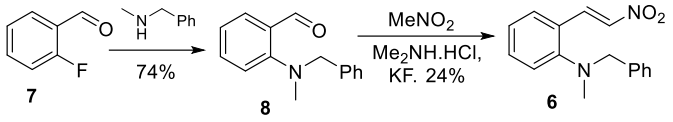
Table 1. Screening of fluorinated alcohols for the [1,5]-H shift nitro-Mannich reaction

Substrate	Solvent	Temp. (°C)	Time (h)	Product	Yield (%)[a]
 **1**	CF_3CH_2OH	78	9.5	 **2**	55
	HFIP	58	4		90
 **3**	HFIP	58	18	 **4**	65
 **5**	HFIP	58	162	-[b]	0
 **6**	HFIP	58	18	-[b]	0

[a]Isolated Yield. [b]Recovered starting material.

A known ethereal substrate **5**[15] was prepared from salicyl aldehyde[16] and subjected to refluxing conditions in HFIP, but gave no product. It has been noted in the literature that acyclic benzyl ethers are harder to isomerise than cyclic ethers.[2n] A corresponding

acyclic amino analogue **6** was prepared by optimisation of the published route to the cyclisation precursor **1** and **3** (Scheme 4).[3] An S_NAr reaction between 2-fluorobenzaldehyde **7** and *N*-methylbenzylamine gave amino aldehyde **8** in 74% yield which was subjected to a Henry reaction to give the cyclisation precursor **6** in 24% yield. Heating in HFIP unfortunately only gave starting material. With the limited substrate window shown by HFIP, we decided to explore the original literature rearrangement **1** to **2** (Scheme 2b) with Lewis acids.



Scheme 4. Synthesis of acyclic amino analogue

Lewis acids $BF_3(OEt)_2$, $TiCl_4$, $Ti(O^iPr)_4$ and $Sc(OTf)_3$ had all shown to be useful for the corresponding [1,5]-H shift and cyclisation with ethers and α,β-unsaturated carbonyls. Treatment of **1** with catalytic and stoichiometric quantities of these in CH_2Cl_2 at rt and reflux gave colour changes and precipitates, but starting material was recovered after aqueous work up. Presumably these particular Lewis acids coordinate to the amine of **1**. We next screened Lewis acids that had been used to catalyse the conjugate addition of nucleophiles to nitroalkenes. However $SnCl_2$,[17] and $Cu(OTf)_2$,[18] gave no product under a variety of conditions. The cyclisation of the corresponding compound with an additional geminal vinyl ester had been achieved with $Mg(OTf)_2$ in refluxing MeCN.[4] While repeat of these conditions on **1** gave no reaction the use of another Lewis acid from this work $Gd(OTf)_3$ (10 mol%) under the same conditions (MeCN, reflux, 18 h) gave the desired product **2** in 33% isolated yield.

A solvent screen was then conducted on a mixture of **1** with 50 mol% $Gd(OTf)_3$ (Table 2). TIBCO Spotfire® was used to visualise principle component analysis (PCA), whereby solvent data from an internal AstraZeneca database was arranged by orthogonal properties.[19] The axes used to portray the solvents in 3D space were not linked to specific properties (e.g. boiling point or dielectric constant), but instead were functions generated from these properties. From this 3D visualisation it was possible to divide solvents which should behave similarly into octants of chemical space and one solvent was picked from each octant to screen. Each reaction was heated to 60 °C for 12 h with aliquots taken at t = 0, 0.33, 0.67, 1, 2, 3, 4, 6, 8 and 12 h and monitored by HPLC (Table 2). As degradation was observed under some conditions the time chosen for comparison was when the percentage area of the product peak was at its greatest for each set of conditions. Whilst MeCN provided the initial result and was the solvent used for a similar rearrangement in the literature,[4] it was observed to perform poorly as a solvent in these conditions with the product peak accounting for 47% of the total peak area. Perhaps surprisingly PhMe appeared to perform best, with a 94% conversion after 12 h and very little side product formation or degradation occurring despite the reaction proceeding more slowly than with MeCN and 2-MeTHF, for example.

Table 2. Solvent screen with $Gd(OTf)_3$ on **1** to give **2** (Scheme 2b)

Solvent	Time (h)	Area of HPLC product peak (%)
DMF	12	0
PhMe	12	94
MeCN	4	47[a]
2MeTHF	3	65[b]
IPA	4	41[b]
p-xylene	12	75[c]
1-hexanol	6	46[b]
Bu_3N	12	0

[a]Major degradation peak. [b]Several other products. [c]20% starting material

Two other lanthanide triflates were surveyed in this reaction; $Yb(OTf)_3$ gave 14% yield by HPLC, whereas $Ce(OTf)_3$ gave no conversion. A control reaction using 5 mol% TfOH also gave no conversion confirming that the Lewis acid $Gd(OTf)_3$ was responsible for catalysing this reaction. The optimum reaction conditions were found to be heating a solution of **1** in PhMe (10.0 mL per mmol) and $Gd(OTf)_3$ (30 mol%) to 100 °C for 12 h to give **2** in 79% isolated yield.

A small library of nitroalkenes were prepared to investigate the limitations of this reaction (Figure 1). The synthesis of the nitroalkenes used either the S_NAr/Henry route from *o*-fluorobenzaldehyde starting materials (Scheme 4) or if that failed the amine was introduced using palladium catalysed amination[20] followed by a Henry reaction from *o*-bromobenzaldehyde starting materials. The substrate tolerance of the two amination reactions and the commercial availability of either the *o*-fluoro- or *o*-bromobenzaldehyde starting materials defined the substrate scope prepared.

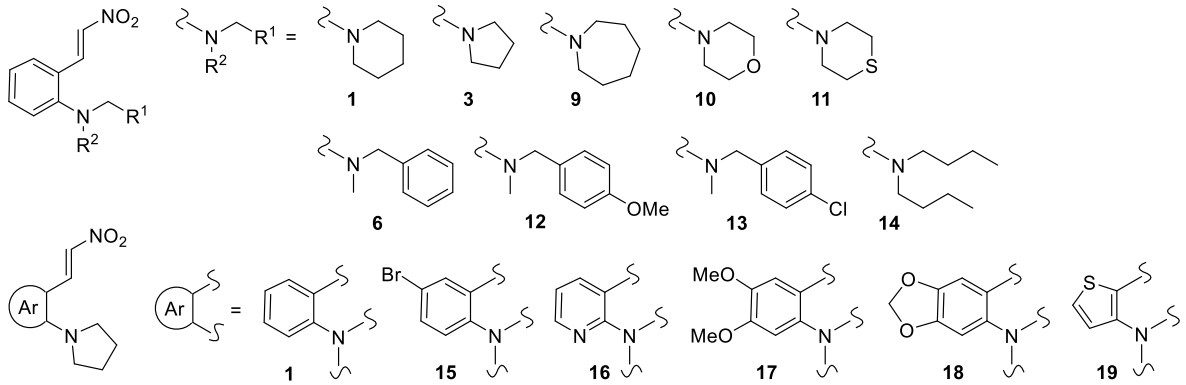
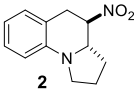
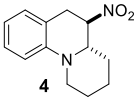
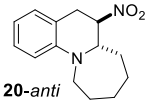
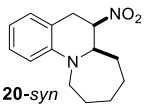
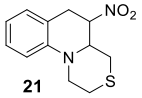
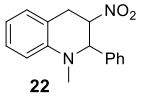
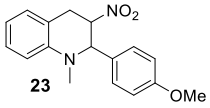
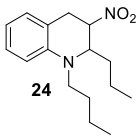
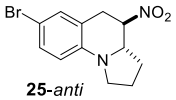
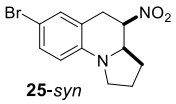
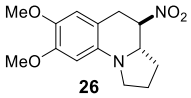
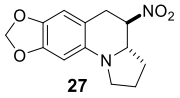
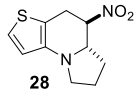


Figure 1. Nitroalkene library

A series of cyclic amines **9**-**11** were synthesised to compare to the successful rearrangement of **1** and **3**. Acyclic variants **12**-**14** were also prepared to compare with **6**. The synthesis of *N*-allyl derivatives was attempted, but were unsuccessful by either of the two routes. Although the desired S_NAr and Palladium catalysed allylations proceeded, albeit in low yield, the subsequent Henry reaction gave complex mixtures of products. The electronics of the aromatic template of **1** were investigated with a series of substituted aromatic and heteroaromatic derivatives **15**-**19**. The nitroalkenes were each treated with 30 mol% $Gd(OTf)_3$ and heated to 100 °C in PhMe for 18 h to give in most cases the desired rearranged products (Table 3). The rearranged products were characterised by 1H NMR. The products lost the vinyl protons associated with the nitroalkene and gained two vicinally coupled protons C*H*NO_2 and NC*H*, diagnostic of the β-nitroamine formed The carbocyclic precursors **1**, **3** and **9** gave good conversions (90, 57 and 67% respectively), but the diastereoselectivity was poor for the 7-membered ring substrate **9** (66:34). Morpholine **10** gave no reaction and thiomorpholine **11** gave a poor 9% yield of rearranged product **21** as a single diastereoisomer after heating for 7 days. The rearrangement of acyclic precursors was successful with the nitroalkenes derived from neutral **6** or electron rich **12** benzylamines and alkylamine **14** giving rearranged products **22**, **23** and **24** in 67, 84 and 74% yields respectively. The *dr* of **23** was 90:10 and **24** was isolated essentially as a single diastereoisomer. In contrast the neutral phenyl product **22** had a crude *dr* of 75:25. The nitroalkene derived from the electron withdrawn chloro-benzylamine **13** took 36 h for complete reaction and gave a major rearranged product that contained a TfO group. We were unable to fully elucidate the structure of this product. The electronic character of the central aromatic template was investigated and the bromosubstituted analogue **25** was formed in 42% yield. The pyridine nucleus **16** gave degradation under the standard conditions and with 1.3 equivalents of $Gd(OTf)_3$ in an attempt to sequester the coordinating ability of the pyridyl nitrogen. The more electron rich derivatives gave the dimethoxy **26**, methylenedioxy **27** and thiophene **28** products in 62, 72 and 25% yields respectively. All of the central aromatic derivatives that rearranged gave products with excellent *dr* and mostly as single diastereoisomers.

Table 3. Substrate scope for the $Gd(OTf)_3$ catalysed [1,5]-H shift nitro-Mannich reaction[a]

Substrate	Product	Yield (%)[b]	*dr*[c]
1	 **2**	79	>95:5
3	 **4**	57	95:5
9	 **20**-*anti*	45	>95:5
	 **20**-*syn*	23	>95:5
10	-	0[d]	-
11	 **21**	9[e]	>95:5
6	 **22**	major 50% minor 17%	>95:5 >95:5
12	 **23**	84	90:10
13	-	0[f]	-
14	 **24**	74	>95:5
15	 **25**-*anti*	38	>95:5
	 **25**-*syn*	4	>95:5
16	-	0[g]	-
17	 **26**	62	>95:5
18	 **27**	72	>95:5
19	 **28**	25	>95:5

[a]Nitroalkene (1 equivalent) and $Gd(OTf)_3$ (30 mol%) were heated in PhMe (10.0 mL per mmol) to 100 °C until the reaction reached completion. [b]Isolated Yield. [c]Measured by 1H NMR. [d]No conversion. [e]Refluxed 7 days. [f]Complete consumption of starting material, unknown product. [g]Degradation.

Characterising the relative stereochemistry was based in part on a single crystal X-ray determination of **26** that confirmed the *anti*-stereochemistry across the nitro amine.[21] The coupling constant across the nitro amine of **26** was ~9.5 Hz, in line with a *trans*-diaxial coupling and similar to the reported value for **2**.[3] The analogues **25**, **27** and **28** have a similary large 9.5, 9.6 and 10.2 Hz *J* value respectively across the nitro amine and were thus assigned the *anti*-stereochemistry. The minor diastereoisomer *syn*-**25** has an expectedly lower corresponding *J* value of 2.7 Hz. The two diastereoisomers of **20** were separable. In the 1H NMR for the major diastereoisomer it was not clear which *J* value of the NC*H* signal δ 4.12 (1H, ddd, *J*=7.6, 6.4, 3.1 Hz) was due to coupling from the C*H*NO_2 proton as it appeared as a multiplet (δ 4.67), as did the two NCHCH_2 protons (δ 1.82-1.87 and 1.58-1.50). However both the nitroamine protons for the minor diastereoisomer were distinct at δ 4.90 (1H, ddd, *J*=12.4, 5.7, 4.3 Hz, $CHNO_2$) and δ 4.08 (1H, dt, *J*=8.5, 4.3 Hz, NCH). The large *J*=12.4 Hz coupling constant of C*H*NO_2 was due to coupling to one of the benzylic protons δ 3.53 (1H, dd, *J* = 16.2, 12.4 Hz). The nitroamine coupling constant was *J*=4.3 Hz. By comparison to the diastereoisomers of **25**, we can tentatively assign the minor diastereoisomer of **20**, *syn* and the major diastereoisomer *anti*, with a corresponding nitroamine coupling constant for the latter of

J=7.6 or 6.4 Hz. Only one diastereoisomer of **4** was isolated with a nitroamine coupling constant *J*=6.2 Hz. We therefore tentatively assign this the *anti*- relative stereochemistry based upon the magnitude of the nitro amine coupling constant and comparison to that of *anti*-**20**. The major diastereoisomer of **21** exhibited a nitroamine coupling constant *J*~5 Hz, which we think is not definitive enough to justify a stereochemical assignment by comparison to **4** and **20**. The coupling constants for the nitroamine of the three compounds **22**-**24** were obscured and/or ambiguous so no structural assignment could be made by 1H NMR.

To demonstrate the use of these compounds for the synthesis of 1,2-diamines, product **2** was subjected to a standard Zn/HCl reduction and trifluoroacetylation which we have used routinely (Scheme 6).[22] The protected diamine was isolated in an unoptimised 46% yield over the two steps. The coupling constant across the 1,2-diamine was identical to that starting material (*J*=9.7) indicating that the *anti*-stereochemistry had been retained

Scheme 6. Formation of 1,2-diamine

3. Conclusion

We have developed two methods for the [1,5]-H shift nitro-Mannich reaction for the synthesis of 2,3-disubstituted tetrahydroquinolines that allows a greater substrate scope for this reaction. HFIP was found to cyclise cyclic amine substrates **1** and **3** under mild conditions (58 °C) to give the tetrahydroquinoline products **2** and **4** in 90% and 65% yields respectively as single diastereoisomers. While examples of the cyclisation of pyrrolidinyl amine **1** have been published in the literature, the cyclisation of the piperidinyl amine **3** had not been achieved. HFIP did not promote the [1,5]-H shift nitro-Mannich reaction of acyclic amines, so an alternative procedure was investigated that used catalytic $Gd(OTf)_3$ in refluxing PhMe. This system was successful for 5-membered (**1**), 6-membered (**3**) and 7-membered (**9**) cyclic amine substrates. Rearrangement of **9** gave **20** which had been prepared in a similar manner by Kim. Our 67% yield and 2:1 *dr* is not as efficient as their results of 98%, 4:1 *dr* with $Sc(OTf)_3$ in MeCN and 68%, *dr* 4:1 with a thiourea catalyst. In contrast and uniquely the $Gd(OTf)_3$ catalysed conditions were able to cyclise acyclic tertiary neutral (**6**) and electron rich benzylic- (**12**) and alkyl- (**14**) amines in high yields with diastereomeric ratios ranging from 75:25 to >95:5. Substituents on the aniline precursors (**15**, **17** and **18**) were on the whole well tolerated with yields ranging from 42-72% and diastereomeric ratios of 90:10 to >95:5. Although the electron poor aniline with a *para*-Br- substituent was the lowest yielding. This, together with the results that the heteroyclic amine derived from morpholine (**10**) and the electron withdrawn benzylic amine **13** possessing a Cl- substituent were both inert to the reaction conditions, emphasised the extent of stabilisation required for the intermediate iminium ion to be formed. The sulphur containing amino substituted thiophene **19** gave only a moderate 25% (*dr* >95:5) of rearranged product **28** and the heteroyclic amine derived from thiomorpholine (**11**) gave a low yield (9%) of **21** after prolonged heating (7 days). The sulphur atom in substrates **11** and **19** could be coordinating to the metal catalyst and leading to other by-products. Preference for the cyclisation to favour the *anti*-diastereoisomer was confirmed from a combination of X-ray and coupling constant data for the product β-nitro-amine function. Overall, conditions for a wider substrate scope have been demonstrated for the [1,5]-H shift nitro-Mannich reaction. The reaction is substrate dependent with a fine balance for iminium ion stability required for rearrangement. Optimisation of different metal catalysts to suit particular substrates and the application of this methodology to natural product synthesis is currently under investigation

4. Experimental Section

4.1. General

All non-aqueous reactions were carried out in oven-dried glassware under an inert atmosphere unless otherwise indicated. All reaction temperatures refer to the values of the external heating element and not that of the reaction mixture. Room temperature implies a temperature range of 20-25 °C. A temperature of 0 °C was achieved using an ice-water bath whereas cryogenic conditions (-78 °C or -68 °C) were achieved using a dry ice and acetone or CH_2Cl_2 bath respectively. All additions of reagent occurred as a single portion or fast unless otherwise stated. Column chromatography was carried out using BDH (40-60 µm) silica gel and analytical thin layer chromatography was carried out using Merck Keiselgel aluminium-backed plates coated with silica gel. Automatic column chromatography was carried on a Biotage® Isolera™ Spektra or CombiFlash® EZ Prep fitted with RediSep® or Biotage® SNAP Ultra cartridges. Components were visualised using ultra-violet light (254 nm) and a basic potassium permanganate dip. Removal of solvent in vacuo was achieved using Büchi rotary evaporators and either the house vacuum or a Büchi Vac® V-500 pump. Where a compound has been prepared using a specific literature procedure, this is referenced by the compound name.

All commercial chemicals and solvents were used as supplied unless otherwise stated. The dry solvents toluene and THF were obtained from a solvent tower, where degassed solvents were passed through two columns of activated alumina and a 7 micron filter under 4 bar pressure. Other anhydrous solvents were purchased bottled from the Aldrich chemical company and used as provided. Activation of 4 Å molecular sieves was achieved by heating under a high vacuum.

Melting points are uncorrected and were obtained using a Reichert Melting Point Apparatus. Infrared (IR) spectra were recorded on a Perkin Elmer spectrum 100 FT-IR (ATR mode). 1H NMR spectra were recorded at 300 MHz on a Bruker Avance 300 spectrometer, at 400 MHz on a Bruker Avance 400 spectrometer, at 500 MHz on a Bruker Avance 500 spectrometer, at 600 MHz on a Bruker Avance 600 spectrometer or at 700 MHz on a Bruker Avance 700 spectrometer in the stated solvent using the residual protic solvent $CHCl_3$ (δ = 7.26 ppm, s) or DMSO (δ = 2.56 ppm, qn) as the internal standard. Chemical shifts are quoted in ppm using the following abbreviations: s, singlet d, doublet t, triplet q, quartet qn, quintet m, multiplet, br, broad or a combination of these. The coupling constants (J) are measured in Hertz. 13C NMR spectra were recorded at 125 MHz on a Bruker Avance 600 Spectrometer or at 175 MHz on a Bruker Avance 700 Spectrometer in the stated solvent using the internal reference of CHCl3 (δ = 77.0 ppm, t) or DMSO (δ = 39.52 ppm, sept) as the internal standard.226 Chemical shifts are reported to the nearest 0.1 ppm. Mass spectrometry data was collected on Thermo Finnigan Mat900xp (EI/CI) VG-70se (FAB) and Waters LCT Premier XE (ES) instruments.

4.2. Synthesis of nitroalkenes

General procedure A for the synthesis of 2-aminobenzaldehydes.

The known 2-aminobenzaldehydes were synthesised by the literature procedure based on the work of Rabong,[3] involving the S_NAr reaction between the requisite fluorobenzaldehydes and amines to give the known precursor benzaldehydes to nitroalkenes **1**,[3] **3**,[16] **6**,[4] **9**,[23] **10**,[24] **12**,[25] **13**,[25] **14**,[26] **15**,[27] and **16**.[28]

General procedure B for the Pd catalysed synthesis of aminobenzaldehydes.

A 2-bromoaryl aldehyde (1 equivalent) was added to a suspension/solution of Cs_2CO_3 (1.4 equivalents), $Pd(OAc)_2$ (0.01 equivalents) and (±)BINAP (0.03 equivalents) in PhMe (10 mL per mmol). The reaction mixture was stirred at rt for 5 min before a secondary amine (1.1 equivalents) was added and the resulting mixture heated to 90 °C (heating block) for 18 h. Following cooling to rt, the solvent was removed *in vacuo* and the crude product was purified by column chromatography to give the known precursor benzaldehydes to nitroalkenes **11**,[24] **17**,[29] and **19**.[30]

General Procedure C for the Synthesis of Nitroalkenes.

The literature procedure by Rabong[3] was optimised. A solution of aldehyde (1 equivalent) in PhMe (5.0 mL per mmol) was added KF (0.19 equivalents), $Me_2NH.HCl$ (1.5 equivalents), $MeNO_2$ (3.5 mL per mmol) and the solution heated to 90 °C (heating block) for 18 h. The solvent was then removed *in vacuo* to give the crude product which was purified by column chromatography.

*4.2.1. (E)-N-Benzyl-N-methyl-2-(2-nitrovinyl)aniline (**6**).* The requisite aldehyde **8**[4] (2.25 g, 10.0 mmol), prepared by General procedure A, was subjected to General procedure C and gave after purification by column chromatography (2% EtOAc/hexane), **6** (761 mg, 28%) as a bright red oil: IR υ_{max} (neat) 3099, 3058, 3025, 2945, 1623, 1593, 1552, 1507 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (1H, d, *J* = 13.8 Hz), 7.64 (1H, d, *J* = 13.8 Hz), 7.52 – 7.48 (1H, m), 7.45 – 7.39 (1H, m), 7.36 – 7.30 (2H, m), 7.27 (3H, m), 7.16 – 7.12 (1H, m), 7.12 – 7.06 (1H, m), 4.13 (2H, s), 2.69 (3H, s); ^{13}C NMR (175 MHz, $CDCl_3$) δ 154.4 (Ar*C*), 137.4, (NCH_2CH_2), 137.1 (Ar*C*), 137.0 (NCH_2CH_2), 132.8 (Ar*C*H), 129.3 (Ar*C*H), 128.7 (Ar*C*H), 128.7 (Ar*C*H), 127.7 (Ar*C*H), 124.7 (Ar*C*), 123.4 (Ar*C*H), 121.1 (Ar*C*H), 62.2 (NCH_2Ph), 41.98 (NCH_3); HRMS (ES) $[M+H]^+$ Calcd for $C_{16}H_{17}N_2O_2$ 269.1290; Found 269.1298.

*4.2.2. (E)-1-(2-(2-Nitrovinyl)phenyl)azepane (**9**).* The requisite aldehyde[23] (690 mg, 3.35 mmol), prepared by General procedure A, was subjected to General procedure C and gave after purification by column chromatography (2% EtOAc/hexane), **9** (477 mg, 58%) as a dark red oil: IR υ_{max} (neat) 3098, 2952, 2912, 2878, 2831, 1624, 1596, 1505 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (1H, d, *J* = 13.7 Hz), 7.58 (1H, d, *J* = 13.7 Hz), 7.44 (1H, dd, *J* = 7.8, 1.6 Hz), 7.41 – 7.36 (1H, m), 7.15 (1H, dd, *J* = 8.3, 0.9 Hz), 7.00 (1H, dd, *J* = 11.1, 3.9 Hz), 3.23 – 3.17 (4H, m), 1.79 (8H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.6 (*C*), 138.2 (*C*H), 136.2 (CH_2), 132.6 (*C*H), 129.0 (*C*H), 123.8 (*C*), 122.0 (*C*H), 120.8 (*C*H), 56.8 (CH_2), 29.3 (CH_2), 27.3 (CH_2); HRMS (ES) $[M+H]^+$ Calcd for $C_{14}H_{19}N_2O_2$ 247.1447; Found 247.1454.

*4.2.3. (E)-4-(2-(2-Nitrovinyl)phenyl)morpholine (**10**).* The requisite aldehyde[23] (368 mg, 1.88 mmol), prepared by General procedure A, was subjected to General procedure C and gave after purification by automated column chromatography (0-10% EtOAc/heptane), **10** (186 mg, 38%) as a dark red oil: : IR υ_{max} (neat) 3099, 3033, 2890, 2849, 1625, 1596 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (1H, d, *J* = 13.8 Hz), 7.67 (1H, d, *J* = 13.8 Hz), 7.53 – 7.44 (2H, m), 7.13 (2H, dd, *J* = 7.7, 6.3 Hz), 3.94 – 3.88 (4H, m), 3.00 – 2.96 (4H, m); ^{13}C NMR (175 MHz, $CDCl_3$) δ 153.8 (Ar*C*), 137.3 (NCH_2CH_2), 136.5 (NCH_2CH_2), 133.1 (Ar*C*H), 129.3 (Ar*C*H), 124.6 (Ar*C*), 123.9 (Ar*C*H), 119.9 (Ar*C*H), 67.2 (OCH_2), 53.6 (NCH_2); HRMS (ES) $[M+H]^+$ Calcd for $C_{12}H_{14}N_2O_3$ 235.1077; Found 235.1071.

*4.2.4. (E)-4-(2-(2-Nitrovinyl)phenyl)thiomorpholine (**11**).* The requisite aldehyde[24] (340 mg, 1.64 mmol), prepared by General procedure B, was subjected to General procedure C and gave after purification by column chromatography (10% EtOAc/hexane), **11** (260 mg, 63%) as a light red crystalline solid: mp 80 – 82 °C; IR υ_{max} (neat) 3098, 2952, 2912, 2878, 2831, 1624, 1596, 1505 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.39 (1H, d, *J* = 13.8 Hz), 7.64 (1H, d, *J* = 13.8 Hz), 7.51 (1H, d, *J* = 7.8 Hz), 7.49 – 7.45 (1H, m), 7.16 – 7.12 (2H, m), 3.26 – 3.20 (4H, m), 2.91 – 2.86 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.0 (*C*), 137.3 (*C*H), 136.3 (*C*H), 133.0 (*C*H), 128.9 (*C*H), 124.9 (*C*), 124.0 (*C*H), 120.8 (*C*H), 55.7 (CH_2), 28.40 (CH_2); HRMS (ES) [M]+ Calcd for $C_{12}H_{14}N_2O_2S$ 250.07705; Found 250.0771.

*4.2.5. (E)-N-(4-Methoxybenzyl)-N-methyl-2-(2-nitrovinyl)aniline (**12**).* The requisite aldehyde[25] (616 mg, 2.40 mmol), prepared by General procedure A, was subjected to General procedure C and gave after purification by column chromatography (10% EtOAc/hexane), **12** (228 mg, 32%) as a red oil: IR υ_{max} (neat) 3097, 3030, 2950, 2832, 2798, 1623, 1609, 1594, 1508 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.52 (1H, d, *J* = 13.8 Hz), 7.65 (1H, d, *J* = 13.8 Hz), 7.50 (1H, dd, *J* = 7.7, 1.4 Hz), 7.46 – 7.39 (1H, m), 7.13 (1H, d, *J* = 8.2 Hz), 7.09 (1H, dd, *J* = 11.4, 4.1 Hz), 6.88 – 6.84 (2H, m), 4.06 (2H, s), 3.80 (3H, s), 2.67 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.1 (*C*), 154.4 (*C*), 137.2 (*C*H), 136.9 (*C*H), 132.8 (*C*H), 130.0 (*C*H), 129.4 (*C*), 129.3 (*C*H), 124.8 (*C*), 123.3 (*C*H), 121.2 (*C*H), 113.9 (*C*H), 61.7 (CH_2), 55.4 (CH_3), 41.6 (CH_3); HRMS (ES) $[M+H]^+$ Calcd for $C_{17}H_{19}N_2O_3$ 299.13174; Found 299.13181.

*4.2.6. (E)-N-(4-Chlorobenzyl)-N-methyl-2-(2-nitrovinyl)aniline (**13**).* The requisite aldehyde[26] (261 mg, 1.00 mmol), prepared by General procedure A, was subjected to General procedure C and gave after purification by column chromatography (10% EtOAc/hexane), **13** (105 mg, 35%) as a red oil: IR υ_{max} (neat) 3102, 3032, 2879, 2800, 1625, 1596, 1553, 1509 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 8.50 (1H, d, *J* = 13.8 Hz), 7.64 (1H, d, *J* = 13.8 Hz), 7.51 (1H, d, *J* = 7.8 Hz), 7.42 (1H, t, *J* = 7.3 Hz), 7.30 (2H, d, *J* = 8.3 Hz), 7.20 (2H, d, *J* = 8.2 Hz), 7.11 (2H, m), 4.09 (2H, s), 2.68 (3H, s); ^{13}C NMR (175 MHz, $CDCl_3$) δ 154.0 (*C*), 137.1 (*C*H), 136.8 (*C*H), 135.8 (*C*), 133.5 (*C*) 132.8 (*C*H), 130.0 (*C*H), 129.3 (*C*H), 128.8 (*C*H), 124.8 (*C*), 123.6 (*C*H), 121.2 (*C*H), 61.4 (CH_2), 42.1 (CH_2); HRMS (ES) $[M+H]^+$ Calcd for $C_{16}H_{16}Cl^{35}N_2O_2$ 303.0900; Found 303.0908.

*4.2.7. (E)-N,N-Dibutyl-2-(2-nitrovinyl)aniline (**14**).* The requisite aldehyde[26] (700 mg, 3.00 mmol), prepared by General procedure A, was subjected to General procedure C and gave after purification by column chromatography (0-2% EtOAc/hexane), **14** (398 mg, 48%) as a red oil: IR υ_{max} (neat) 2953, 2927, 2858, 1623, 1593, 1509 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.41 (1H, d, *J* = 13.8 Hz), 7.65 (1H, d, *J* = 13.8 Hz), 7.49 (1H, dd, *J* = 7.8, 1.3 Hz), 7.43 – 7.40 (1H, m), 7.17 (1H, d, *J* = 8.2 Hz), 7.07 (1H, t, *J* = 7.7 Hz), 3.03 – 2.99 (4H, m), 1.44 (4H, tt, *J* = 7.7, 6.5 Hz), 1.30 – 1.22 (4H, m), 0.86 (6H, t, *J* = 7.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.4 (*C*), 137.4 (*C*H), 136.7 (*C*H), 132.26 (*C*H), 129.3 (*C*), 126.1 (*C*H), 123.1 (*C*H), 122.5 (*C*H), 54.5 (CH_2), 29.6 (CH_2), 20.5 (CH_2), 14.0 (CH_3); HRMS (ES) $[M+H]^+$ Calcd for $C_{16}H_{25}N_2O_2$ 277.1916; Found 277.1921.

*4.2.8. (E)-1-(4-Bromo-2-(2-nitrovinyl)phenyl)pyrrolidine (**15**).* The requisite aldehyde[27] (530 mg, 2.09 mmol), prepared by General procedure A, was subjected to General procedure C and gave after purification by automated column chromatography (0-

10% EtOAc/heptane), **15** (242 mg, 39%) as a red crystalline solid: mp 88 – 89 °C; IR υ_{max} (neat) 3112, 2987, 2950, 2922, 2851, 1607, 1588, 1551, 1530 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.33 (1H, d, *J* = 13.4 Hz), 7.46 (1H, d, *J* = 2.4 Hz), 7.42 (1H, d, *J* = 13.4 Hz), 7.37 (1H, dd, *J* = 8.9, 2.4 Hz), 6.75 (1H, d, *J* = 9.0 Hz), 3.35 (4H, m), 2.01 – 1.96 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.1 (*C*), 138.3 (*C*H), 135.4 (*C*H), 135.0 (*C*H), 131.8 (*C*H), 119.9 (*C*), 117.4 (*C*H), 110.9 (*C*), 52.9 (CH_2), 25.8 (CH_2); HRMS (ES) $[M]^+$ Calcd for $C_{12}H_{23}BrN_2O_2$ 297.0239; Found 297.0248.

*4.2.9. (E)-3-(2-Nitrovinyl)-2-(pyrrolidin-1-yl)pyridine (**16**).* The requisite aldehyde[28] (584 mg, 3.35 mmol), prepared by General procedure A, was subjected to General procedure C and gave after purification by column chromatography (20% EtOAc/hexane), **16** (282 mg, 30%) as a bright red crystalline solid: mp 64 – 66 °C; IR υ_{max} (neat) 3176, 3104, 2983, 2958, 2876, 2859, 1683, 1607, 1586, 1545 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.36 (1H, d, *J* = 13.3 Hz), 8.25 (1H, dd, *J* = 4.6, 1.8 Hz), 7.59 (1H, dd, *J* = 7.6, 1.6 Hz), 7.37 (1H, d, *J* = 13.3 Hz), 6.68 (1H, dd, *J* = 7.6, 4.7 Hz), 3.65 – 3.60 (4H, m), 1.99 – 1.94 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.4 (*C*), 151.3 (*C*H), 138.8 (*C*H), 138.0 (*C*H), 135.1 (C*H*), 113.5 (*C*H), 110.6 (*C*), 51.3 (CH_2), 25.9 (CH_2);; HRMS (ES) $[M+H]^+$ Calcd for $C_{11}H_{14}N_3O_2$ 220.1086; Found 220.1112.

*4.2.10. (E)-1-(4,5-Dimethoxy-2-(2-nitrovinyl)phenyl)pyrrolidine (**17**).* The requisite aldehyde[29] (353 mg, 1.50 mmol), prepared by General procedure B, was subjected to General procedure C and gave after purification by column chromatography (20% EtOAc/hexane), **17** (259 mg, 62%) as a dark purple crystalline solid: mp 136 – 138 °C; IR υ_{max} (neat) 3118, 2964, 2918, 2862, 2848, 2826, 1625, 1584, 1569, 1546, 1517 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.45 (1H, d, *J* = 13.3 Hz), 7.45 (1H, d, *J* = 13.2 Hz), 6.83 (1H, s), 6.45 (1H, s), 3.93 (3H, s), 3.86 (3H, s), 3.36 – 3.33 (4H, m), 2.04 – 1.96 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.9 (*C*), 148.5 (*C*), 143.3 (*C*), 138.8 (*C*H), 132.4 (*C*H), 111.1 (*C*), 110.7 (*C*H), 99.9 (*C*H), 56.4 (CH_3), 56.0 (CH_3), 53.6 (CH_2), 25.6 (CH_2); HRMS (ES) $[M+H]^+$ Calcd for $C_{14}H_{19}N_2O_4$ 279.1345; Found 279.1347.

*4.2.11. (E)-1-(6-(2-Nitrovinyl)benzo[d][1,3]dioxol-5-yl)pyrrolidine (**18**).* The requisite aldehyde was prepared by General procedure B: 6-bromopiperonal (460 mg, 2.02 mmol) gave the aldehyde (375 mg, 86%) as a yellow crystalline solid after purification by column chromatography (20% EtOAc/hexane): mp 71 – 73 °C; IR υ_{max} (neat) 2969, 2945, 2865, 1627, 1604, 1493 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 10.01 (1H, s), 7.22 (1H, s), 6.44 (1H, s), 5.94 (2H, s), 3.40 – 3.35 (4H, m), 2.02 – 1.96 (4H, m). ^{13}C NMR (150 MHz, $CDCl_3$) δ 188.1 (*C*H), 153.7 (*C*), 150.6 (*C*) 140.6 (*C*), 117.4 (*C*), 108.6 (*C*H), 101.7 (CH_2), 95.8 (*C*H), 54.0 (CH_2), 26.0 (CH_2); HRMS (ES) $[M+H]^+$ Calcd for $C_{12}H_{14}NO_3$ 220.0974; Found. 220.0979.

The requisite aldehyde (334 mg, 1.53 mmol) was subjected to General procedure C and gave after purification by column chromatography (10% EtOAc/hexane), **18** (140 mg, 36%) as a red crystalline solid: mp 91 – 93 °C; IR υ_{max} (neat) 3128, 2950, 2917, 2835, 2678, 1596, 1502 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.41 (1H, d, *J* = 13.3 Hz), 7.40 (1H, d, *J* = 13.3 Hz), 6.84 (1H, s), 6.55 (1H, s), 5.96 (2H, s), 3.27 (4H, m), 2.00 – 1.95 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.5 (*C*), 150.1 (*C*), 142.1 (*C*), 138.7 (*C*H), 132.8 (*C*H), 112.8 (*C*), 106.9 (*C*H), 101.8 (CH_2), 98.1 (*C*H), 53.9 (CH_2), 25.5 (CH_2). HRMS (ES) $[M+H]^+$ Calcd for $C_{13}H_{15}N_2O_4$ 263.1032; Found 263.1040.

*4.2.12. (E)-1-(2-(2-Nitrovinyl)thiophen-3-yl)pyrrolidine (**19**).* The requisite aldehyde[30] (170 mg, 0.94 mmol), prepared by General procedure B, was subjected to General procedure C and gave after purification by column chromatography (10% EtOAc/hexane), **20** (259 mg, 62%) as a yellow crystalline solid: mp 157 – 159 °C; IR υ_{max} (neat) 3087, 2959, 2922, 2852, 1534 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.56 (1H, dd, *J* = 12.2, 1.0 Hz), 7.37 (1H, dd, *J* = 5.7, 1.1 Hz), 7.22 (1H, d, *J* = 12.2 Hz), 6.56 (1H, d, *J* = 5.7 Hz), 3.65 – 3.61 (4H, m), 2.12 – 2.05 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.0 (*C*), 135.0 (*C*H), 132.5 (*C*H), 127.6 (*C*H), 119.9 (*C*H), 105.3 (*C*), 52.2 (CH_2), 25.8 (CH_2). HRMS (ES) $[M+H]^+$ Calcd for $C_{10}H_{13}N_2O_2S$ 225.0698; Found 225.0115.

4.3. [1,5]-H shift cyclisations

*4.3.1. (3a**S***,4**R***)-4-Nitro-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinolone (**2**).* A solution of **1** (60 mg, 0.27 mmol) in HFIP (4 mL) was heated to 58 °C (heating block) for 4 h then cooled to rt and the solvent removed *in vacuo* to give a crude residue which was purified by column chromatography (2% EtOAc in hexane) to give diastereomerically pure **2**[3] (54 mg, 90%) as a yellow crystalline solid: mp 94 – 95 °C.

Alternatively **1** (1 mmol) could be rearranged using $Gd(OTf)_3$ according to general procedure D below to give diastereomerically pure **2**[3] (79%).

*4.3.2. (4a**S***,5**R***)-5-Nitro-2,3,4,4a,5,6-hexahydro-1H-pyrido[1,2-a]quinolone (**4**).* In an identical procedure for the formation of **2**, nitroalkene **3** (92 mg, 0.40 mmol) was rearranged in HFIP over 18 h to give diastereomerically pure **4** (53 mg, 58%) as a low melting waxy solid: IR υ_{max} (neat) 2938, 2850, 1597, 1576, 1540 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.18 – 7.15 (1H, td, *J* = 8.3, 0.8 Hz), 7.05 (1H, d, *J* = 7.3 Hz), 6.84 (1H, d, *J* = 8.3 Hz), 6.76 (1H, td, *J* = 7.4, 0.8 Hz), 4.70 (1H, ddd, *J* = 7.7, 6.2, 5.1 Hz), 3.95 – 3.89 (1H, m), 3.54 (1H, ddd, *J* = 10.8, 6.2, 2.5 Hz), 3.44 (1H, dd, *J* = 15.5, 7.8 Hz), 3.16 (1H, dd, *J* = 15.5, 5.0 Hz), 2.83 (1H, td, *J* = 12.6, 2.9 Hz), 1.95 – 1.88 (1H, m,H), 1.80 – 1.72 (1H, m), 1.69 – 1.44 (4H, m,H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.3 (*C*), 129.2 (*C*H), 128.3 (*C*H), 120.0 (*C*), 118.8 (*C*H), 113.1 (*C*H), 86.4 (*C*H), 59.0 (*C*H), 48.1 (CH_2), 31.5 (CH_2), 30.1 (CH_2), 24.5 (CH_2), 24.1 (CH_2); HRMS (ES) $[M+H]^+$ Calcd for $C_{13}H_{17}N_2O_2$ 233.1290; Found: 233.1305. Data in agreement with the literature.[3]

Alternatively **3** (0.25 mmol) could be rearranged using $Gd(OTf)_3$ according to general procedure D below to give **4** (79%) as an inseparable 95:5 mixture of diastereoisomers.

General procedure D for 1,5-hydride shift nitro-Mannich cyclisation using $Gd(OTf)_3$.

Nitroalkene (1 equivalent) and $Gd(OTf)_3$ (0.3 equivalents) were heated in toluene (10.0 mL per mmol) to 100 °C until the reaction reached completion (18 h unless otherwise stated). The toluene was then removed *in vacuo* and the resultant residue purified via column chromatography to give the cyclised product.

*4.3.3. (**20**)-anti (6**R***,6a**S***)- and (**20**)-syn (6**R***,6a**R***)- 6-Nitro-5,6,6a,7,8,9,10,11-octahydroazepino[1,2-a]quinolone.* The nitroalkene **9** (90 mg, 0.37 mmol) was subjected to General procedure D and gave a crude 66:34 mixture of diastereoisomers. Purification by column chromatography (5% EtOAc/hexane) gave **20**-*anti* (6*R**,6a*S**) (39 mg, 45%) as a yellow oil; IR υ_{max} (neat) 3025, 2923, 2858, 1602, 1578, 1540, 1499 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.10 (1H, t, *J* = 7.8 Hz), 7.06 (1H, d, *J* = 7.4 Hz), 6.66 (1H, t, *J* = 7.3 Hz), 6.60 (1H, d, *J* = 8.3 Hz), 4.69 – 4.67 (1H, m), 4.12 (1H, ddd, *J* = 7.6, 6.4, 3.1 Hz), 3.85 (1H, ddd, *J* = 15.3, 5.9, 2.9 Hz), 3.54 (1H, d, *J* = 17.8 Hz), 3.21 (1H, dd, *J* = 17.8, 5.4 Hz), 3.11 (1H, ddd, *J* = 15.6, 10.6, 5.3 Hz), 2.11 – 2.03 (1H, m), 1.87 – 1.82 (1H, m), 1.72 – 1.59 (4H, m), 1.58 – 1.50 (1H, m), 1.48 – 1.40 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.0 (*C*), 129.2 (*C*H), 128.0 (*C*H), 116.5 (*C*H), 116.0 (*C*), 111.0 (*C*H), 81.9 (*C*H), 60.6 (*C*H), 49.4 (CH_2), 33.5 (CH_2), 27.4 (CH_2), 27.2 (CH_2), 26.1

(*C*H$_2$), 25.9 (*C*H$_2$). HRMS (ES) [M+H]$^+$ Calcd for $C_{14}H_{19}N_2O_2$ 247.1447; Found 247.1461; and **20**-*syn* (6*R**,6a*R**) (21 mg, 23%) as a yellow oil; IR υ_{max} (neat) 3021, 2930, 2903, 2855, 1600, 1574, 1530, 1494 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.12 (1H, t, *J* = 7.7 Hz), 7.08 (1H, t, *J* = 6.8 Hz), 6.67 (1H, td, *J* = 7.4, 0.7 Hz), 6.62 (1H, d, *J* = 8.3 Hz), 4.90 (1H, ddd, *J* = 12.4, 5.7, 4.3 Hz), 4.08 (1H, dt, *J* = 8.5, 4.3 Hz), 3.92 (1H, ddd, *J* = 15.1, 6.1, 3.1 Hz), 3.53 (1H, dd, *J* = 16.2, 12.4 Hz), 3.27 – 3.16 (2H, m), 2.15 – 2.06 (1H, m), 1.72 – 1.47 (6H, m), 1.43 – 1.33 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.9 (*C*), 129.9 (*C*H), 128.3 (*C*H), 116.6 (*C*H), 116.1 (*C*), 110.8 (*C*H), 81.1 (*C*H), 60.0 (*C*H), 49.9 (*C*H$_2$), 28.7 (*C*H$_2$), 27.0 (*C*H$_2$), 26.7 (*C*H$_2$), 26.2 (*C*H$_2$), 25.6 *C*H$_2$).

*4.3.4. 5-nitro-1,2,4,4a,5,6-hexahydro-[1,4]thiazino[4,3-a]quinolone (**21**).* The nitroalkene **11** (100 mg, 0.40 mmol) was subjected to General procedure D for 7 days and after purification by column chromatography (10% EtOAc/hexane) gave diastereomerically pure **21** (9 mg, 9%) as a low melting waxy solid: IR υ_{max} (neat) 2955, 2913, 2890, 2850, 2825, 1596, 1563, 1507 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17 (1H, td, *J* = 8.3, 1.5 Hz), 7.09 (1H, d, *J* = 7.2 Hz), 6.80 (1H, td, *J* = 7.4, 0.8 Hz), 6.76 (1H, d, *J* = 8.3 Hz), 4.67 (1H, q, *J* = 5.0 Hz), 4.34 (1H, dddd, *J* = 11.0, 4.4, 2.0, 1.1 Hz), 4.29 (1H dt, *J* = 14.5, 2.8 Hz), 3.48 – 3.42 (2H, m, ArC*H*$_2$), 3.15 (1H, dd, *J* = 16.6, 5.2 Hz), 3.03 (1H, ddd, *J* = 13.5, 12.2, 2.7 Hz), 2.80 (1H, dd, *J* = 13.0, 11.0 Hz), 2.39 (1H, d, *J* = 13.0 Hz), 2.31 (1H, ddd, *J* = 13.4, 4.0, 2.5 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.9 (*C*), 129.4 (*C*H), 128.5 (*C*H), 119.6 (*C*), 119.1 (*C*H), 113.5 (*C*H), 83.9 (*C*H), 60.5 (*C*H), 50.1 (*C*H$_2$), 28.8 (*C*H$_2$), 28.2 (*C*H$_2$), 23.4 (*C*H$_2$); HRMS (ES) [M+H]$^+$ Calcd for $C_{12}H_{15}N_2O_2S$ 251.0854; Found 251.0858.

*4.3.5. 1-Methyl-3-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline (**22**).* The nitroalkene **6** (109 mg, 0.41 mmol) was subjected to General procedure D and gave a crude 75:25 mixture of diastereoisomers. Purification by column chromatography (10% EtOAc/hexane) gave **22**-major (55 mg, 50%) as a yellow solid: mp 93 – 94 °C; IR υ_{max} (neat) 3060, 3026, 2895, 2827, 1601, 1576, 1546, 1497 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.28 (3H, m), 7.23 – 7.18 (3H, m), 7.03 (1H, d, *J* = 7.3 Hz), 6.72 (2H, m), 5.19 (1H, apparent singlet), 4.84 (1H, apparent dd, *J* = 7.8, 3.9 Hz), 3.42 (1H, ddd, *J* = 16.8, 3.7, 1.4 Hz), 3.01 (1H, dd, *J* = 16.8, 4.4 Hz); ^{13}C NMR (175 MHz, $CDCl_3$) δ 144.4 (*C*), 139.5 (*C*), 129.3 (*C*H), 129.0 (*C*H), 128.5 (*C*H), 128.4 (*C*H), 126.6 (*C*H), 117.3 (*C*H), 110.6 (*C*H), 83.8 (*C*H), 64.8 (*C*H), 37.8 (*C*H$_3$), 27.6 (*C*H$_2$); HRMS (ES) [M+H]$^+$ Calcd for $C_{16}H_{17}N_2O_2$ 269.1290 Found: 269.1986; and **22**-minor (18 mg, 17%) as a yellow oil: IR υ_{max} (neat) 3025, 2895, 2833, 1602, 1577, 1542, 1499 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.29 (3H, m), 7.28 (1H, d, *J* = 7.8 Hz), 7.12 (1H, d, *J* = 7.4 Hz), 7.03 (2H, dt, *J* = 3.7, 2.1 Hz), 6.75 (1H, td, *J* = 7.4, 0.9 Hz), 6.72(1H, d, *J* = 8.2 Hz), 5.30 (1H, m), 5.18 (1H, m), 3.25 – 3.22 (1H, m), 3.19 – 3.15 (1H, m), 2.92 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3 (*C*), 135.7 (*C*), 129.3 (*C*H), 128.5 (*C*H), 128.5 (*C*H), 128.3 (*C*H), 127.1 (*C*H), 116.8 (*C*H), 116.3 (*C*H), 109.8 (*C*H), 81.5 (*C*H), 64.5 (*C*H), 37.6 (*C*H$_3$), 26.4 (*C*H$_2$).

4.3.6. (2S,3R*)-2-(4-Methoxyphenyl)-1-methyl-3-nitro-1,2,3,4-tetrahydroquinoline (**23**).* The nitroalkene **12** (114 mg, 0.38 mmol) was subjected to General procedure D and after purification by column chromatography (10% EtOAc/hexane) gave **23** (96 mg, 84%) as an inseparable 90:10 mixture of diastereoisomers as a low melting orange waxy solid: IR υ_{max} (neat) 2927, 2833, 1603, 1575, 1508 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20 – 7.16 (1H, m), 7.07 – 7.03 (2H, m), 6.87 – 6.84 (2H, m), 6.82 (1H, d, *J* = 7.6 Hz), 6.72 (1H, d, *J* = 8.3 Hz), 6.68 (1H, td, *J* = 7.5, 1.0 Hz), 4.90 (1H, td, *J* = 6.6, 3.4 Hz), 4.80 (1H, d, *J* = 6.6 Hz), 3.79 (3H, s), 3.77 (1H, ddd, *J* = 11.9, 6.7, 1.1 Hz), 3.58 (1H, dd, *J* = 12.0, 3.4 Hz), 2.99 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.0 (*C*), 145.3 (*C*), 133.6 (*C*), 130.4 (*C*H), 130.1 (*C*H), 128.3 (*C*H), 121.7 (*C*), 118.1 (*C*H), 114.4 (*C*H), 111.7 (*C*H), 85.8 (*C*H), 55.4 (*C*H$_3$), 51.2 (*C*H$_2$), 46.4 (*C*H), 39.3 (*C*H$_3$); HRMS (ES) [M+2H-OCH$_3$]$^+$ Calcd for $C_{16}H_{17}N_2O_2$ 269.1290 Found: 269.1294

*4.3.7. 1-Butyl-3-nitro-2-propyl-1,2,3,4-tetrahydroquinoline (**24**).* The nitroalkene **14** (83 mg, 0.30 mmol) was subjected to General procedure D and after purification by column chromatography (0-2% EtOAc/hexane) gave diastereomerically pure **24** (61 mg, 74%) as a yellow oil: IR υ_{max} (neat) 3036, 2954, 292, 2868, 1601, 1575, 1544, 1498 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.10 (1H, t, *J* = 7.8 Hz), 7.07 (1H, d, *J* = 7.3 Hz), 6.68 (1H, td, *J* = 7.4, 0.8 Hz), 6.58 (1H, d, *J* = 8.3 Hz), 4.75 (1H, m), 4.04 (1H, m), 3.52 (1H, d, *J* = 18.1 Hz), 3.43 (1H, ddd, *J* = 14.6, 9.7, 5.0 Hz), 3.12 (1H, dd, *J* = 18.1, 5.6 Hz), 2.99 (1H, ddd, *J* = 14.7, 9.8, 6.4 Hz), 1.60 (2H, ddd, *J* = 10.2, 6.8, 2.7 Hz), 1.55 – 1.34 (4H, m), 1.33 – 1.25 (2H, m), 0.97 (3H, td, *J* = 7.2, 2.6 Hz), 0.93 (3H, t, *J* = 7.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.5 (*C*), 129.2 (*C*H), 127.7 (*C*H), 117.0 (*C*), 116.7 (*C*H), 111.9 (*C*H), 81.1 (*C*H), 60.8 (*C*H), 50.9 (*C*H$_2$), 34.4 (*C*H$_2$), 29.8 (*C*H$_2$), 26.2 (*C*H$_2$), 20.2 (*C*H$_2$), 19.4 (*C*H$_2$), 14.2 (*C*H$_3$), 14.1 (*C*H$_3$); Calcd for $C_{16}H_{25}N_2O_2$ 277.19160 Found: 277.19169.

*4.3.8. (**25**)-anti (3aS*,4R*) and (**25**)-syn (3aR*,4R*) -7-Bromo-4-nitro-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinolone.* The nitroalkene **15** (118 mg, 0.397 mmol) was subjected to General procedure D and gave a crude 90:10 mixture of diastereoisomers. Purification by column chromatography (5% EtOAc/hexane) gave **25**-*anti* (3a*S**,4*R**) (45 mg, 38%) as an orange crystalline solid: mp 138 °C (dec.); IR υ_{max} (neat) 2971, 2946, 2856, 1595, 1532, 1495 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22 (1H, dd, *J* = 8.6, 1.9 Hz), 7.16 (1H, s), 6.36 (1H, d, *J* = 8.6 Hz), 4.42 (1H, ddd, *J* = 12.0, 9.7, 4.7 Hz), 3.76 (1H, td, *J* = 9.6, 5.5 Hz), 3.47 – 3.41 (2H, m), 3.27 – 3.21 (m, 2H), 2.25 (1H, ddd, *J* = 12.3, 6.9, 1.4 Hz), 2.16 (1H, ddd, *J* = 12.8, 9.7, 7.5 Hz), 2.06 – 1.96 (1H, m), 1.77 (1H, tdd, *J* = 11.9, 9.5, 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.1 (*C*), 131.4 (*C*H), 131.1 (*C*H), 119.4 (*C*), 112.7 (*C*H), 108.2 (*C*), 83.9 (*C*H), 60.4 (*C*H), 47.8 (*C*H$_2$), 33.4 (*C*H$_2$), 30.8 (*C*H$_2$), 23.5 (*C*H$_2$); HRMS (ES) [M]$^+$ Calcd for $C_{12}H_{13}BrN_2O_2$ 297.0239; and **25**-*syn* (3a*R**,4*R**) (5 mg, 4%) as an orange crystalline solid: mp 137 °C (dec.); IR υ_{max} (neat) 2970, 2946, 2855, 1594, 1532, 1495 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 (dt, *J* = 11.1, 5.6 Hz, 1H), 7.16 – 7.14 (m, 1H), 6.40 (d, *J* = 8.6 Hz, 1H), 5.11 (dt, *J* = 5.1, 2.7 Hz, 1H), 3.74 (ddd, *J* = 9.2, 6.3, 2.7 Hz, 1H), 3.39 (td, *J* = 8.8, 3.4 Hz, 1H), 3.33 – 3.26 (m, 3H, NC*H*$_2$), 2.22 (dtd, *J* = 9.5, 6.9, 2.8 Hz, 1H), 2.10 – 2.03 (m, 1H), 2.03 – 1.95 (m, 1H), 1.86 – 1.78 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.8 (*C*), 131.1 (*C*H), 130.5 (*C*H), 118.7 (*C*), 112.9 (*C*H), 108.5 (*C*), 78.7 (*C*H), 58.5 (*C*H), 47.3 (*C*H$_2$), 31.6 (C*H*$_2$), 28.4 (*C*H$_2$), 23.1 (*C*H$_2$).

4.3.9. (3aS,4R*)-7,8-Dimethoxy-4-nitro-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinolone (**26**).* The nitroalkene **17** (111 mg, 0.40 mmol) was subjected to General procedure D and after purification by column chromatography (20% EtOAc/hexane) gave diastereomerically pure **26** (69 mg, 62%) as an orange crystalline solid: mp 163-164 °C; IR υ_{max} (neat) 2989, 2938, 2919, 2878, 1618, 1592, 1535, 1521 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.63 (1H, s), 6.14 (1H, s), 4.45 (1H, ddd, *J* = 11.8, 9.8, 4.9 Hz), 3.87 (3H, s), 3.81 (3H, s), 3.72 (1H, td, *J* = 9.2, 5.7 Hz), 3.47 (1H, td, *J* = 8.6, 3.0 Hz), 3.42 (1H, ddd, *J* = 14.9, 11.9, 0.7 Hz), 3.29 (1H, dd, *J* = 16.0, 8.4 Hz), 3.20 (1H, dd, *J* = 15.0, 4.9 Hz), 2.25 – 2.20 (1H, m), 2.16 – 2.09 (1H, m), 2.06 – 1.96 (1H, m), 1.82 – 1.75 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.4 (*C*), 140.9 (*C*), 138.0 (*C*), 113.7 (*C*H), 108.5 (*C*), 97.3 (*C*H), 84.8 (*C*H), 60.4 (*C*H), 57.0 (*C*H$_3$), 56.1 (*C*H$_3$), 48.5 (*C*H$_2$), 33.3 (*C*H$_2$), 30.6 (*C*H$_2$), 23.5 (*C*H$_2$); HRMS (ES) [M+H]$^+$ Calcd for $C_{14}H_{19}N_2O_4$ 279.1345

Found: 279.1345 m.p. 163-164 °C. Relative stereochemistry was from single crystal X-ray diffraction, see ESI.

4.3.10. (3aS,4R*)-4-Nitro-1,2,3,3a,4,5-hexahydro-[1,3]dioxolo[4,5-g]pyrrolo[1,2-a]quinolone (**27**).* The nitroalkene **18** (100 mg, 0.38 mmol) was subjected to General procedure D and after purification by column chromatography (10% EtOAc/hexane) gave diastereomerically pure **27** (72 mg, 72%) as a yellow crystalline solid: mp 166-168 °C; IR υ_{max} (neat) 2981, 2942, 2895, 2870, 2836, 2782, 1625, 1614, 1540, 1502 cm^{-1} ^1H NMR (600 MHz, $CDCl_3$) δ 6.57 (1H, s), 6.16 (1H, s), 5.85 (2H, dd, *J* = 3.3, 1.3 Hz), 4.43 (1H, ddd, *J* = 11.8, 9.7, 4.9 Hz), 3.70 (1H, td, *J* = 9.3, 5.7 Hz), 3.40 (2H, ddd, *J* = 11.9, 9.0, 4.6 Hz), 3.24 (1H, dd, *J* = 16.1, 8.5 Hz), 3.17 (1H, dd, *J* = 15.1, 4.9 Hz), 2.24 – 2.18 (1H, m), 2.14 – 2.08 (1H, m), 2.03 – 1.94 (1H, m), 1.77 (1H, tt, *J* = 11.1, 8.4 Hz); ^{13}C NMR (150 MHz,$CDCl_3$) δ 147.7 (*C*), 139.0 (*C*), 138.7 *C*), 109.0 (*C*H), 109.0 (*C*), 100.8 (CH_2), 94.4 (*C*H), 84.7 (*C*H), 60.4 (*C*H), 48.7 (CH_2), 33.8 (CH_2), 30.6 (CH_2), 23.4 (CH_2); HRMS (ES) $[M+H]^+$ Calcd for $C_{13}H_{15}N_2O_4$ 263.1032 Found: 263.1029.

*4.3.11. 5-nitro-4,5,5a,6,7,8-hexahydrothieno[3,2-e]indolizine (**28**).* The nitroalkene **19** (36 mg, 0.15 mmol) was subjected to General procedure D and after purification by column chromatography (10% EtOAc/hexane) gave diastereomerically pure **28** (9 mg, 25%) as a low melting white waxy solid: IR υ_{max} (neat) 3324, 3295, 2912, 2865, 1715, 1669, 1602, 1547, 1506 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.64 (1H, d, *J* = 5.6 Hz), 6.72 (1H, d, *J* = 5.6 Hz), 4.52 – 4.48 (ddd, *J* = 10.6, 6.0, 3.2 Hz), 4.46 (1H, dd, *J* = 10.2, 7.0 Hz), 3.96 (1H, d, *J* = 15.7 Hz), 3.60 – 3.55 (1H, m), 3.35 – 3.25 (1H, m), 3.21 (1H, dd, *J* = 15.7, 3.5 Hz), 2.12 (1H, dt, *J* = 12.5, 6.4 Hz), 2.06 (1H, dt, *J* = 9.7, 4.3 Hz), 2.03 – 1.98 (1H, m), 1.78 (1H, dd, *J* = 12.2, 5.7 Hz); ^{13}C NMR too faint to analyse; HRMS (ES) $[M+H]^+$ Calcd for $C_{10}H_{13}N_2O_2S$ 225.0692 Found: 225.0701.

*4.3.12. 2,2,2-Trifluoro-N-((anti)-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinolin-4-yl)acetamide (**29**).* A solution of HCl (6 M, 1.2 mL) was added dropwise to a solution of **2** (75 mg, 0.34 mmol) in EtOAc/EtOH (1:1, 10 mL) at 0 °C. Zinc dust (223 mg) was added and the yellow mixture was stirred for 30 min. The colourless reaction mixture was then quenched with sat. aq. $NaHCO_3$ (sat.) and the resultant white precipitate filtered through a short pad of Celite and washed with EtOAc (30 mL). The aqueous layer was separated and extracted with EtOAc (30 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo* to give the crude amine as a colourless oil which was used directly.

To the crude amine from above in CH_2Cl_2 (7.0 mL) at -78 °C was added DIPEA (0.18 mL, 1.0 mmol) and TFAA (0.14 mL, 1.0 mmol), the mixture stirred for 10 min and then warmed to rt. The reaction mixture was diluted with water (7.0 mL), separated and the aqueous layer extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The resultant crude material was purified by column chromatography (30% EtOAc in hexane) to give **29** as an off-white low melting point waxy solid (45 mg, 46%): IR υ_{max} (neat) 3220, 3066, 2927, 2844, 171, 1602, 1555, 1502 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.11 (1H, t, *J* = 7.6 Hz), 6.99 (1H, d, *J* = 7.4 Hz), 6.61 (1H, t, *J* = 7.3 Hz), 6.44 (1H, d, *J* = 8.1 Hz), 6.12 (1H, s), 4.08 (1H, ddd, *J* = 11.9, 9.7, 5.1 Hz), 3.40 (1H, td, *J* = 8.9, 2.1 Hz), 3.34 (1H, td, *J* = 9.9, 5.3 Hz), 3.29 (1H, dd, *J* = 16.4, 8.8 Hz), 3.08 (1H, dd, *J* = 15.2, 4.9 Hz), 2.84 (1H, dd, *J* = 15.1, 11.9 Hz), 2.18 – 2.08 (2H, m), 1.92 (1H, dtd, *J* = 15.6, 12.2, 8.9 Hz), 1.75 (1H, ddd, *J* = 21.5, 11.7, 7.4 Hz); ^{13}C NMR (175 MHz, $CDCl_3$) δ 143.8 (*C*), 129.0 (*C*H), 128.2 (*C*H), 118.6 (*C*), 116.2 (*C*H), 110.8 (*C*H), 62.2 (*C*H), 49.6 (*C*H), 47.6 (CH_2), 34.9 (CH_2), 31.2 (CH_2), 23.6 (CH_2); HRMS (ES) $[M+H]^+$ Calcd for $C_{14}H_{16}F_3N_2O$ 285.1209; Found 285.1215

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Supplementary Material

General experimental details, copies of 1H and 13C NMR spectra for new compounds and X-ray data.