An Asymmetric Intramolecular Conjugate Addition nitro-Mannich route to *cis*-2-aryl-3-nitrotetrahydroquinolines

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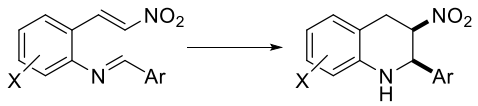
Supporting Information Placeholder

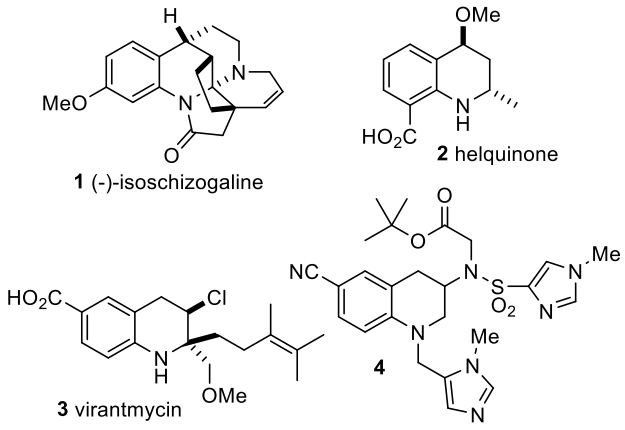


12 examples
88-100% yield
88-99% *ee*

Reductive cyclisation of 2-imino-nitrostyrenes (from the condensation of 2-aminostyrenes with an aldehyde and subsequent nitration of the alkene) using a bifunctional thiourea catalyst and ᵗbutyl-Hantzsch ester leads to an intramolecular conjugate hydride addition nitro-Mannich reaction to give the corresponding *cis*-2-aryl-3-nitrotetrahydroquinolines as single diastereoisomers, in high yields and enantioselectivities.

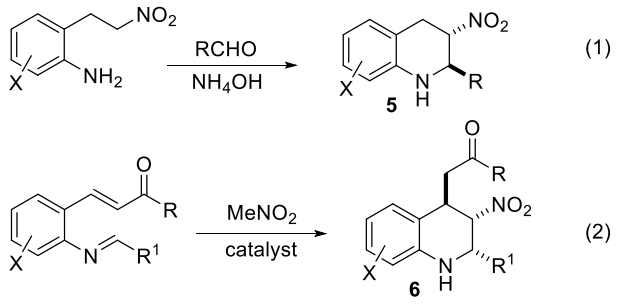
Tetrahydroquinolines are present in numerous biologically active natural products and drug substances.[1] Natural products (-)-isoschizogaline (**1**)[2] and helquinone (**2**)[3] display antibiotic activity, the drug molecule viratmycin (**3**)[4] is an antiviral antibiotic that also possesses antifungal activity, while drug molecule **4**[5] is an antimalarial (Figure 1).

Figure 1. Biologically active tetrahydroquinolines



The efficient synthesis of functionalised tetrahydroquinolines in enantiomerically pure form continues to be of high importance to synthetic chemists.[1] For flexible syntheses in terms of stereochemistry and functionalization, *de novo* constructions of the heterocycle are the most efficient methods. Of those methods, the intramolecular cyclisation of a resonance stabilized nucleophile onto an imine derived from an aniline has proved most popular.[6] In particular, the nitro-Mannich cyclisation of nitronate nucleophiles onto a pendant aniline imine gives highly versatile stereodefined nitro-substituted tetrahydroquinolines (Scheme 1). The nitro group is a versatile synthetic handle and can be transformed into amines, carbonyl groups or be denitrated.[7] The nitro-Mannich reaction is an efficient route to stereochemically pure β-nitroamines which have been shown to be useful building blocks for amino heterocycles.[8] We devised a diastereoselective intramolecular nitro-Mannich route to *trans*-3-nitrotetrahydroquinolines **5** in racemic form *via* in situ generation of an imine from 2-(2-nitroethyl)phenylamine (Scheme 1, equation 1).[9] This has recently shown to be amenable to asymmetric control through the use of a bifunctional tertiary amine thiourea catalyst that gave products with moderate to good enantioselectivities.[10] Other routes to enantiomerically pure nitrotetrahydroquinolines have also taken advantage of organocatalysis. A tandem Michael–nitro-Mannich sequence gave *cis*, *trans*-nitrotetrahydroquinolines **6** (Scheme 1, equation 2),[11] a structural motif that can also be made with the *trans*, *trans* stereochemistry by an aza-Michael–Michael strategy using nitroalkenes.[12] The *cis*-diastereoisomer of **5** can also be prepared by chiral phosphoric acid catalyzed transfer hydrogenation of 2-aryl-3-nitroquinolines, but this is limited by the poor yields of the multistep synthesis required to prepare the quinolines.[13] We wish to report an efficient asymmetric synthesis of *cis*-2-aryl-3-nitrotetrahydroquinolines *via* an intramolecular nitro-Mannich reaction initiated by an organocatalyzed reduction of the parent nitrostyrene.

Scheme 1. Relevant reported work

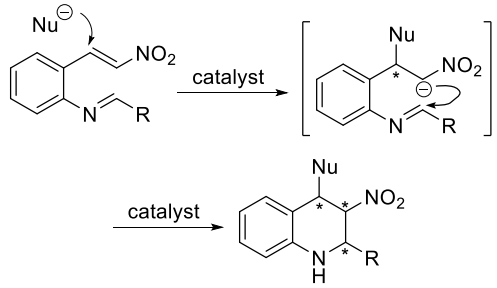


(1)

(2)

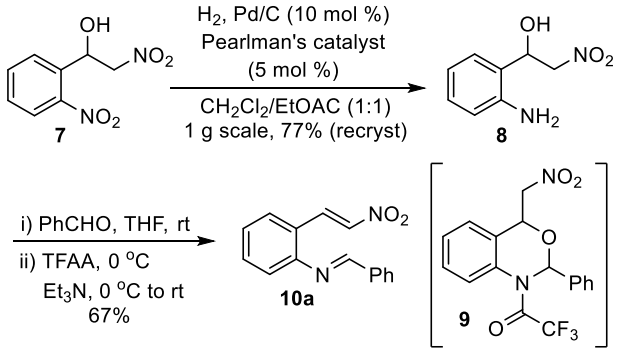
Following on from our work defining stereoselective nitro-Mannich reactions initiated by conjugate addition to nitroalkenes,[14] we reasoned that conjugate addition of a nucleophile to an imino-nitrostyrene would trigger an intramolecular nitro-Mannich reaction to form contiguous stereocentres, with high diastereo- and enantiocontrol (Scheme 2).

Scheme 2. Proposed reaction



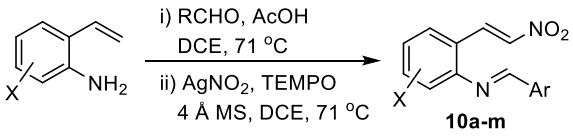
To investigate this reaction, a synthesis of the 2-imino-nitrostyrene precursors was required. The most direct method would be from a 2-amino-β-nitrostyrene and an aldehyde. Attempts at the chemoselective reduction of 2-nitro-β-nitrostyrene were unsuccessful, suffering from reduction of the nitrostyrene. This suggested to us that the reactive nitrostyrene group should be introduced last. After some optimization, our initial approach involved imine formation from the intermediate Henry product between nitromethane and 2-aminobenzaldehyde (**7**, Scheme 3). Selective reduction of the aromatic nitro group of **7** was reliably achieved on a gramme scale using a mixture of palladium on charcoal and Pearlman's catalyst to give **8** in 77% yield after recrystallization.[15] Formation of the imine *in situ* was followed by dehydration of the nitroalcohol to form the desired 2-imino nitrostyrene. Many dehydrating systems were investigated and we found that careful treatment of **8** with trifluoroacetic anhydride and triethylamine minimised retro-Henry reaction and formation of by-product **9** and gave **10a** in good 67% isolated yield. Unfortunately, this sequence gave poor yields (20-30%) with electron rich and poor aldehydes, presumably because with the former the amine lone pair is not nucleophilic enough due to the electron withdrawing nitrostyrene group, and the latter giving mainly byproducts like **9** due to the increased electrophilicity of the formed imine towards cyclisation.

Scheme 3: Initial approach

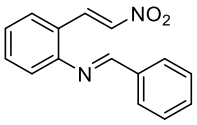


To circumvent this, the desired 2-imino-nitrostyrenes **10a-m** from quantitative imine formation were subjected to late stage nitration.[16] The stereoselective nitration of styrene alkenes had been disclosed by Maiti *et al*. and had been reported to be tolerant of various functional groups.[17] Our results suggest that aromatic imines are also stable to the mild reaction conditions of $AgNO_2$/TEMPO. For the imine derived from pentanal, imine formation proceeded as expected, but nitration unfortunately led to decomposition. Various 2-imino-nitrostyrenes were synthesized according to this procedure (Figure 1) in excellent yield. Substituents on the styrene partner were limited due to the availability of the starting materials. The 5-chloro substituent was tolerated (**10m**), but other electron withdrawing groups in this position (CN, F) were unable to form the imine. This was also true of the 4-chloro analogue and 2-amino-3-vinylpyridine. However a wide variety of electron rich and poor imines were prepared in good yield.

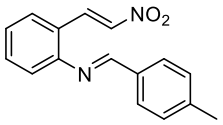
Figure 1. Synthesis of nitrostyrene substrates



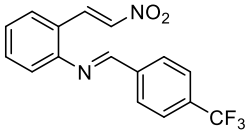
10a-m



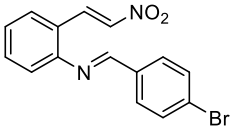
10a, 97% yield



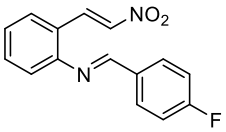
10b, 94% yield

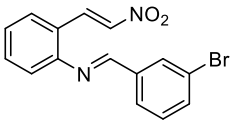


10c, 95% yield

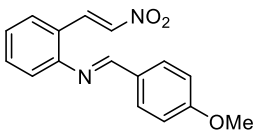


10d, 44% yield

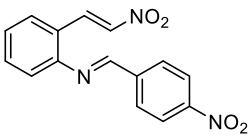




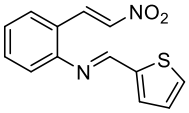
10e, 94% yield



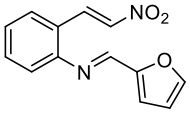
10f, 95% yield



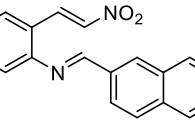
10g, 51% yield



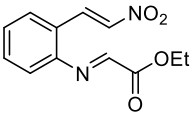
10h, 82% yield



10i, 86% yield



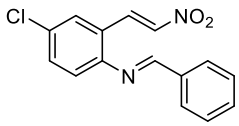
10j, 88% yield



10k, 73% yield

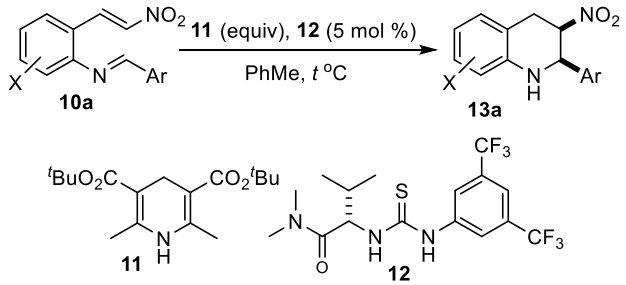
10l, 15% yield

10m, 93% yield



Initially, cyclisation of **10a** was investigated using the conditions previously described by us for the enantioselective tandem reduction/nitro-Mannich reaction.[14e] Using *t*butyl-Hantzsch ester (**11**) as a transfer hydrogenation agent in the presence of thiourea catalyst **12**[14e] the desired tetrahydroquinoline **13a** was isolated in quantitative yield, as a single diastereoisomer by ^{1}H NMR in 94% *ee* (Table 1). No reduction of the imine was observed. Decreasing the temperature from rt to 0 °C gave a small increase in *ee* with increased reaction time (entry 2). Using an equimolar quantity of **11** gave the same yield, *ee* and *dr*.

Table 1. Investigation into cyclisation conditions[a]



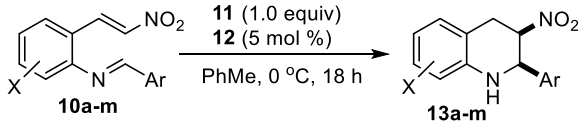
entry	*t* (°C)	11 (eq)	T (h)	yield (%)[b]	ee (%)[c]	dr[d]
1	rt	2	12	99	94	>95:5
2	0	2	18	99	97	>95:5
3	0	1	18	99	97	>95:5

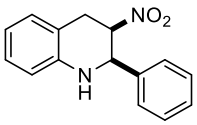
[a]Reaction scale (0.1 mmol), PhMe (1 mL). [b]Isolated yield. [c]Determined by chiral HPLC (OD column). [d]Determined by ^{1}H NMR analysis of crude product.

The generality of the procedure for the synthesis of *cis*-2-aryl-3-nitrotetrahydroquinolines **13** was investigated (Figure 3). All cis-tetrahydroquinolines **13** were made in good yield, high *ee* and essentially as a single diastereoisomer by ^{1}H NMR. The sense of diastereoselectivity was determined by inspection of ^3J coupling constants between the vicinal protons adjacent to the pendant phenyl ring and the nitro function where $^3J_{cis}$ ~4 Hz.[18] The absolute configuration was assigned as 2*R*, 3*R* by comparison to the optical rotations reported by Zhou *et al*.[13,19,20] The diastereoselectivity can be attributed to the *cis*-diastereoisomer being the kinetic product as treatment of *cis*-tetrahydroquinoline **13a** with DBU (1 equiv) in CH_2Cl_2 for 16 h at rt gave a 9:1 mixture in favour of the thermodynamic *trans*-diastereoisomer.[21] This was isolated in 72% yield and possessed identical enantioselectivity to the starting material.[22] This route to the *trans*-products would deliver superior enantioselectivites than other methods.[10]

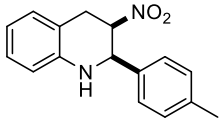
The presence of groups on the *meta*- or *para*- position led to an increase in *ee* but no obvious stereoelectronic preference could be discerned. When Ar = *p*-$NO_2C_6H_5$ the desired product **13h** was not observed, the product from conjugate reduction of the nitrostyrene was isolated instead. This is most probably due to the imine function not participating in the nitro-Mannich reaction due to the lower reactivity of the imine lone pair, the protonation of which is required for the nitro-Mannich reaction to proceed.[21]

Figure 3. Asymmetric Tandem reductive intramolecular nitro-Mannich reaction[a]

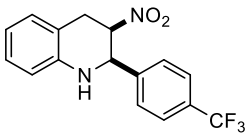


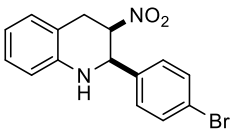


13a, 93% yield, 97% *ee*

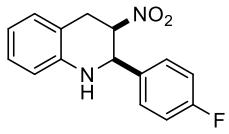


13b, 100% yield, >99% *ee*

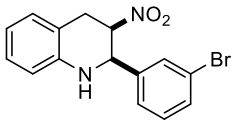




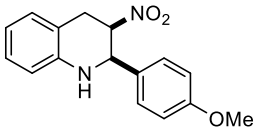
13c, 95% yield, >99% *ee*



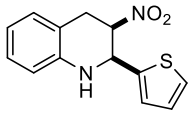
13d, 99% yield, 98% *ee*



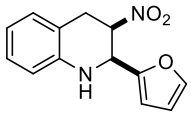
13e, 100% yield, >99% *ee*



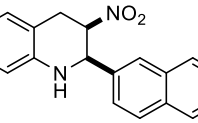
13f, 100% yield, 96% *ee*



13g, 97% yield, 99% *ee*



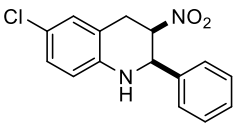
13i, 97% yield, 99% *ee*



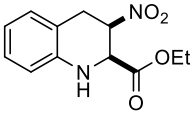
13j, 88% yield, 88% *ee*

13k, 100% yield, 98% *ee*

13l, 93% yield, 93% *ee*



13m, 88% yield[b]



[a]Reaction scale (0.1 mmol) in PhMe (1 mL), isolated yield is given in all cases, *ee was* determined by chiral HPLC (OD column) and diastereoselectivity by ^{1}H NMR analysis. [b]Product unstable to HPLC conditions.

In summary we have developed an expedient synthesis of sensitive 2-imino-nitrostyrenes **10** through the use of radical alkene nitration, which exemplifies the mild nature and further scope of this reaction. These can be cyclised by an organocatalytic tandem reductive nitro-Mannich reaction in high yield to give a single *cis*-2-aryl-3-nitrotetrahydroquinolines **13** in high yield and enantioselectivity. Further investigation is ongoing into the utility of these nitrostyrenes for the synthesis of densely functionalized tetrahydroquinolines of biological interest.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedure, characterization data, NMR spectra for new compounds and HPLC analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

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15. Use of Pearlman's catalyst alone gave 50% yield. Using a 1:1 mixture of 10% Pd/C and Pearlman's catalyst, which has been reported to give superior results for *N*- and *O*- hydrogenolysis of benzyl groups (Li, Y.; Manickam, G.; Ghoshal, A.; Subramaniam, P. *Synth. Commun.* **2006**, *36*, 925), gave little change in yield.
16. The 2-amino-styrenes were prepared from the corresponding 2-nitrophenylacetic acids by the sequence of: reduction of the carboxylic acid to the alcohol with borane, reduction of the nitro group to the amine with Zn, $CaCl_2$ and H_2O, and dehydration by heating with KOH. See Supporting Information. Other structurally diverse substrates have been prepared in the literature by a modified Suzuki reaction between 2-bromoanilines and potassium

vinyltrifluoroborate, see: a) Ascic, E.; Buchwald, S.L. *J. Am. Chem. Soc.* **2015**, *137*, 4666. (b) Li, B.; Park, Y.; Chang, S. *J. Am. Chem. Soc.* **2013**, *135*, 1125.
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18. Compared to $^{3}J_{trans}$ ~8 Hz, see ref 9.
19. Comparison of optical rotations gives the opposite sign and similar values to those in ref 13. Novel tetrahydroquinolines were assigned the same 2*R*, 3*R* stereochemistry by the sign of their optical rotation. See Supporting Information.
20. A transition state model to account for the sense of enantioselectivity would be similar to that proposed by us for the acyclic tandem reduction/nitro-Mannich reaction of nitroalkenes (see SI of ref 13e).
21. We have presented a transition state model to account for the kinetic *cis*-diastereoselectivity versus the thermodynamic *trans*-stereochemistry previously (ref 9).
22. Retention of enantioselectivity in the epimerisation of this substrate was also documented by Zhou *et al*. ref 13 in 74% yield.