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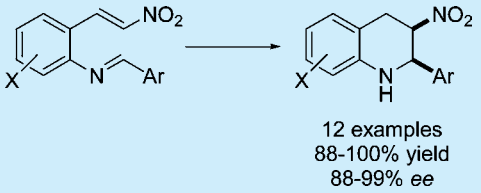
Asymmetric Intramolecular Conjugate Addition Nitro-Mannich Route to *cis*-2-Aryl-3-nitrotetrahydroquinolines

James C. Anderson,* Joshua P. Barham, and Christopher D. Rundell

Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, U.K.

Supporting Information

ABSTRACT: Reductive cyclization of 2-iminonitrostyrenes (from the condensation of 2-aminostyrenes with an aldehyde and subsequent nitration of the alkene) using a bifunctional thiourea catalyst and *tert*-butyl-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, and drug molecule **4**[5] is an antimalarial (Figure 1).

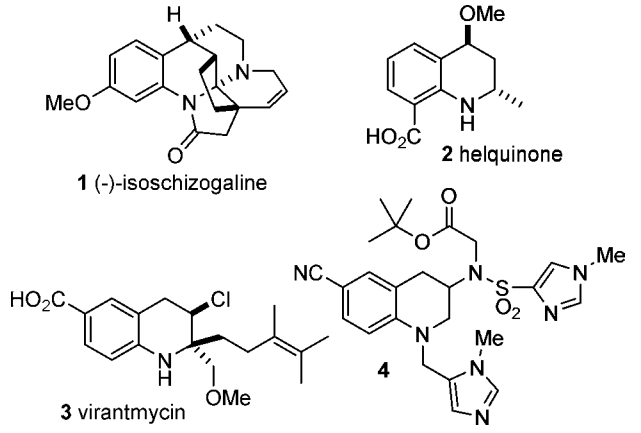
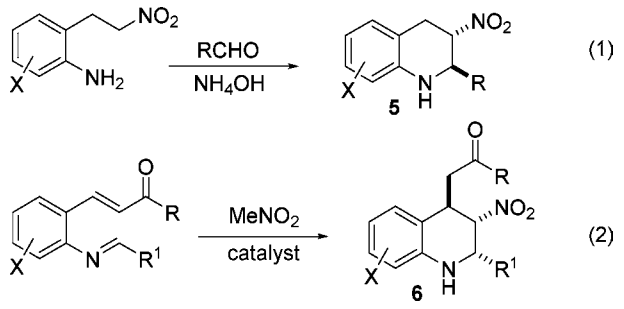


Figure 1. Biologically active tetrahydroquinolines.

The efficient synthesis of functionalized 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 cyclization of a resonance-stabilized nucleophile onto an imine derived from an aniline has proven most popular.[6] In particular, the nitro-Mannich cyclization 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 or 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

Scheme 1. Relevant Reported Work



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, eq 1).[9] This has recently been 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, eq 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.

Following on from our work defining stereoselective nitro-Mannich reactions initiated by conjugate addition to nitro-

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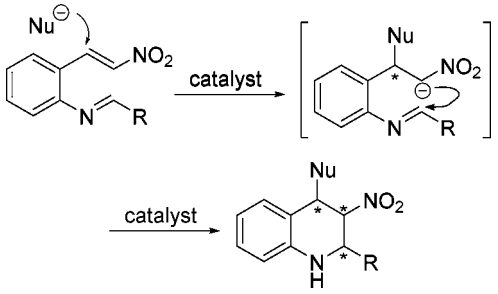
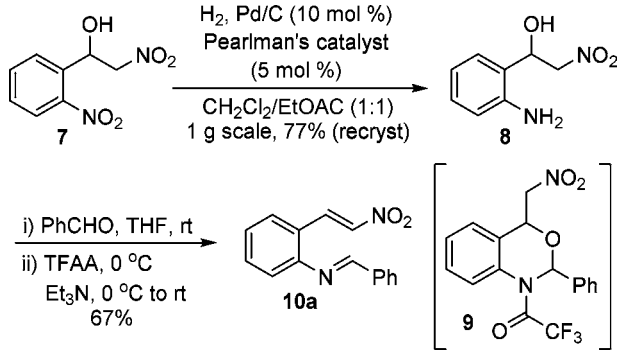
alkenes,[14] we reasoned that conjugate addition of a nucleophile to an iminonitrostyrene would trigger an intramolecular nitro-Mannich reaction to form contiguous stereocenters with high diastereo- and enantiocontrol (Scheme 2).

Scheme 2. Proposed Reaction



To investigate this reaction, a synthesis of the 2-iminonitrostyrene 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

Scheme 3. Initial Approach



of the aromatic nitro group of **7** was reliably achieved on a gram 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-iminonitrostyrene. Many dehydrating systems were investigated, and we found that careful treatment of **8** with trifluoroacetic anhydride and triethylamine minimized retro-Henry reaction and formation of byproduct **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 gives mainly byproducts like **9** due to the increased electrophilicity of the formed imine toward cyclization.

To circumvent this, the desired 2-iminonitrostyrenes **10a−m** from quantitative imine formation were subjected to late-stage nitration (Figure 2).[16] The stereoselective nitration of styrene alkenes had been disclosed by Maiti et al. and had been

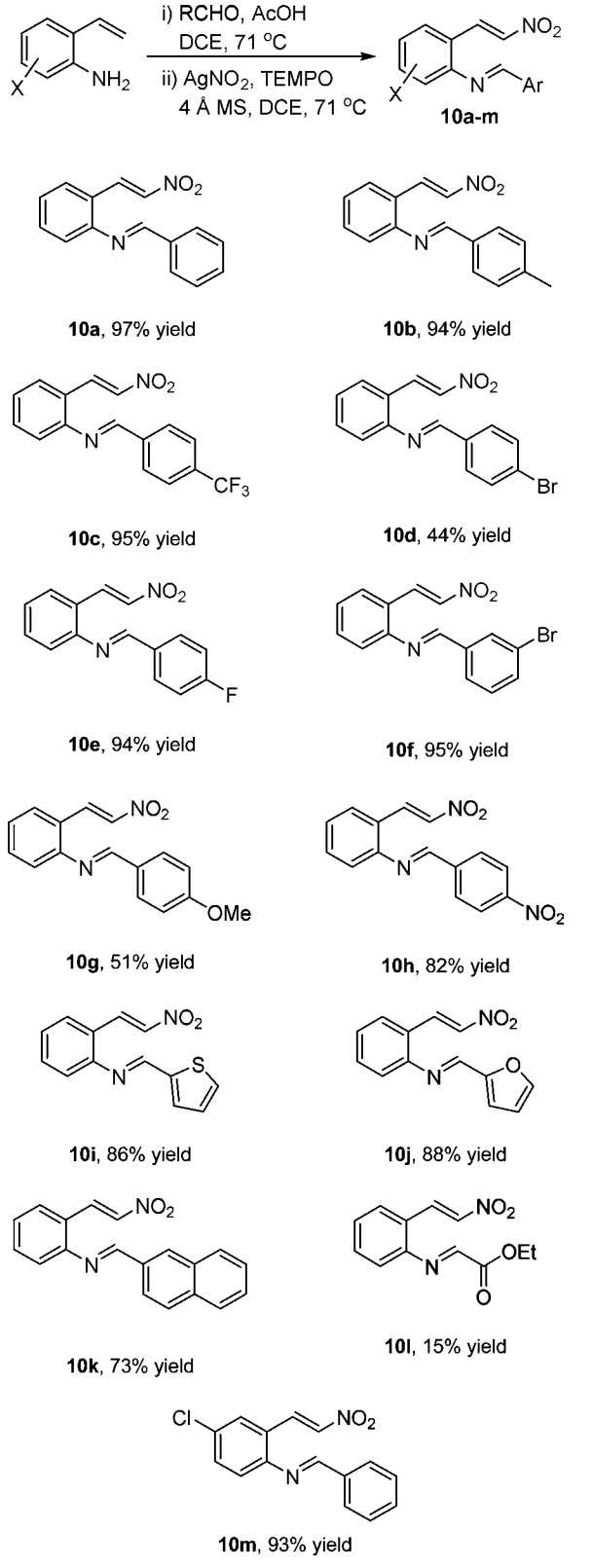


Figure 2. Synthesis of nitrostyrene substrates.

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-iminonitrostyrenes were synthesized according to this

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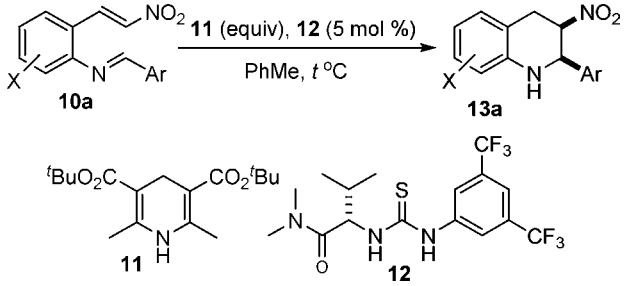
procedure (Figure 1) in excellent yield. Substituents on the styrene partner were limited due to the availability of the starting materials. The 5-chloro substituent was tolerated (**10m**), but other electron-withdrawing groups in this position (CN, F) were unable to form the imine. This was also true 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.

Initially, cyclization of **10a** was investigated using the conditions previously described by us for the enantioselective tandem reduction/nitro-Mannich reaction.[14e] When *tert*-butyl-Hantzsch ester (**11**) was used 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

Table 1. Investigation into Cyclization Conditions[a]



entry	temp (°C)	**11** (equiv)	time (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.

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.

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 $^3J_{cis} \sim 4$ 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 favor 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

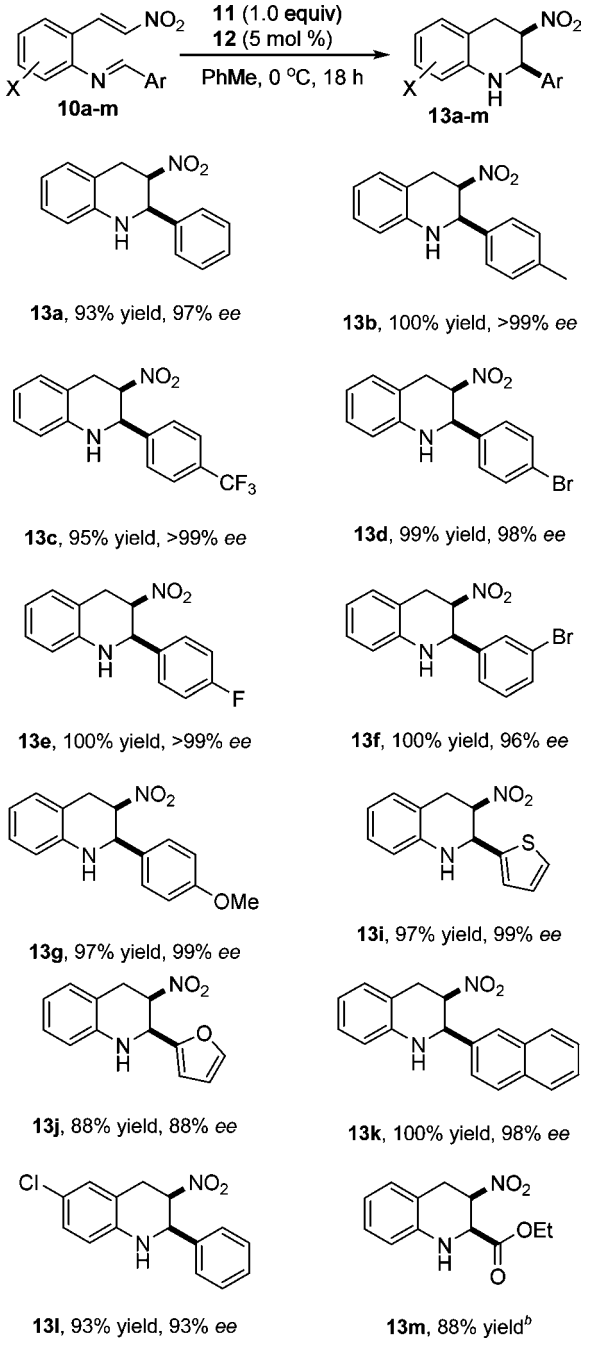


Figure 3. Asymmetric tandem reductive intramolecular nitro-Mannich reaction. (a) Reaction scale (0.1 mmol) in PhMe (1 mL), isolated yield is given in all cases; ee was determined by chiral HPLC (OD column) and diastereoselectivity by ^{1}H NMR analysis. (b) Product unstable to HPLC conditions.

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]

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

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of densely functionalized tetrahydroquinolines of biological interest.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02036.

Detailed experimental procedure, characterization data, NMR spectra for new compounds, and HPLC analysis (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: j.c.anderson@ucl.ac.uk.

Notes

The authors declare no competing financial interest.

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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, gave little change in yield: Li, Y.; Manickam, G.; Ghoshal, A.; Subramaniam, P. *Synth. Commun.* **2006**, *36*, 925.

(16) The 2-aminostyrenes were prepared from the corresponding 2-nitrophenylacetic acids by the following sequence: 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 the 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.* **2014**, *135*, 1125.

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(18) Compared to $^3J_{trans} \sim 8$ Hz; see ref 9.

(19) Comparison of optical rotations gives the opposite sign and values similar to those in ref 13. Novel tetrahydroquinolines were assigned the same 2*R*,3*R* stereochemistry by the sign of their optical rotation. See the 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 the Supporting Information of ref 14e).

(21) We have presented a transition-state model to account for the kinetic *cis*-diastereoselectivity versus the thermodynamic *trans*-stereochemistry previously described (ref 9).

(22) Retention of enantioselectivity in the epimerization of this substrate was also documented by Zhou et al.[13] in 74% yield.

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