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# The First Catalytic, Enantioselective Aza-Henry Reaction of an Unactivated Cyclic Imine

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**Abstract:** The aza-Henry reaction is an efficient route to important chiral, vicinal diamines. Reports of the asymmetric version typically use electron-deficient acyclic imines. We report the first example of a catalytic, asymmetric aza-Henry reaction on an unfunctionalized cyclic imine that gives access to enantiopure diamine derivatives under experimentally straightforward conditions. The stereocentre is established through the initial nitromethane addition to the imine. The scalemic intermediate may be trapped through acylation, then crystallized.

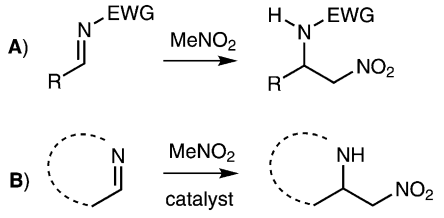
**Keywords:** asymmetric catalysis; aza-Henry reaction; bifunctional catalysis; nitroalkanes; thioureas

Since the first report of diastereo-[1] and enantioselectivity[2] in the aza-Henry (nitro-Mannich) reaction, there has been a great deal of interest in catalytic, enantioselective variants.[3] The interest is primarily because the aza-Henry reaction products, β-nitro amines, can be transformed into chiral vicinal diamines that are fundamentally important compounds in natural products synthesis, pharmaceuticals and as ligands in asymmetric catalysis.[4,5]

Reports to date of the catalytic, enantioselective aza-Henry reaction have described a limited substrate scope, in that acyclic, electron-deficient imines are the ubiquitous electrophile.[3] Cyclic imines present a greater challenge, and the reaction is unknown in such cases. There are remarkably few examples of the catalytic, asymmetric addition of any C-centered nucleophiles to aza-aromatics,[6] but fewer still of addition to cyclic imines with such reactions typically requiring pre-activation of the imine *via* acylation[7] (in some cases oxidatively pre-formed *in situ*[8]) or alkylation[9] or the synthesis of the corresponding *N*-oxide[10,11] or azomethine imine.[12] The exception is Itoh's methodology for the allylation of dihydroisoquinoline[13] and Ohsawa's Mannich reaction on electron-deficient dihydro-beta-carbolines[14] which *prima facie* require no activation of the imine. The aza-Henry reaction (Scheme 1, **A**) employs nitromethane as nucleophile, a reagent with great potential as a replacement for cyanide in asymmetric Strecker-like processes.[15,16] Yet, beyond our recent report of the racemic addition of nitromethane to 3,4-dihydroisoquinoline (DHIQ)[17] the addition of nitromethane to cyclic imines (Scheme 1, **B**) has not been shown beyond a racemic addition to activated isoquinoline[18] and a recent addition to electron-deficient trifluoromethyl ketimines.[19]

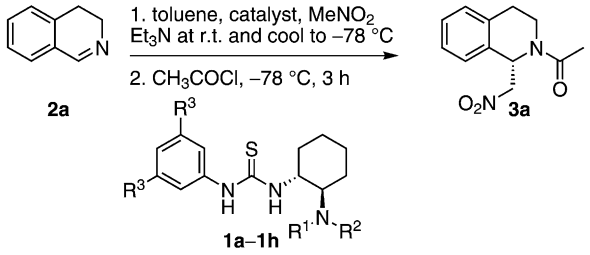
Towards the goal of asymmetric addition of nitromethane to a simple cyclic imine, we initially pursued an approach based on Jacobsen's counterion catalysis concept[20,21] combining thiourea catalysis and alkyl salts of DHIQ. Pre-formation of a reactive electrophile was assumed to be necessary to overcome the likely reversibility of the reaction between DHIQ and nitromethane. However, catalysts that had proven to be successful in related reactions[22] were ineffective for the present reaction with low yields and enantioselectivities being obtained despite a number of variations in catalyst structure.

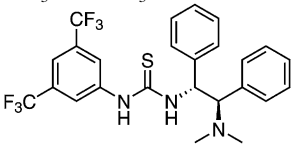
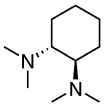
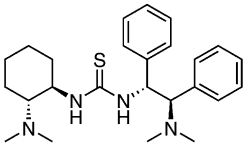
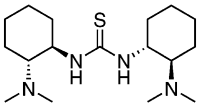
Switching to the Takemoto ligand[23] **1a** gave a promising result of 60% yield of the aza-Henry reaction product **3a** with 68% *ee* in a convenient one-




**Scheme 1.** Aza-Henry reaction of common (**A**) and cyclic (**B**) imines.

**Table 1.** Optimization of catalyst structure.[a]




| Entry | 1 | $R^1$ | $R^2$ | $R^3$ | Yield[b] [%] | *ee*[c] [%] |
|---|---|---|---|---|---|---|
| 1 | – | | | | 16 | <1 |
| 2 | **a** | $CH_3$ | $CH_3$ | $CF_3$ | 60 | 68 |
| 3 | **b** | H | H | $CF_3$ | 34 | 7 |
| 4 | **c** | $C_2H_5$ | $C_2H_5$ | $CF_3$ | 9 | 12 |
| 5 | **d** | $CH_3$ | *i*-Pr | $CF_3$ | 41 | 10 |
| 6 | **e** | *i*-Bu | *i*-Bu | $CF_3$ | 17 | 7 |
| 7 | **f** | Ac | Ac | $CF_3$ | 20 | -2 |
| 8 | **g** | H | *t*-BuSO | $CF_3$ | 86 | 31 |
| 9 | **h** | $CH_3$ | $CH_3$ | H | 49 | 36 |
| 10 | **i** |  | | | 60 | 44 |
| 11 | **j** |  | | | 15 | 4 |
| 12 | **k** |  | | | 47 | 44 |
| 13 | **l** |  | | | 43 | 77 |

[a] Reaction was conducted with **2a** (1 equiv.), catalyst (20 mol%), toluene (0.5 mL), $MeNO_2$ (9 equiv.), $Et_3N$ (1.5 equiv.) and $CH_3COCl$ (3 equiv.).

[b] Yields were quantified using a calibration plot based on the analytical HPLC trace.

[c] Enantiomeric excess was determined by HPLC analysis of **3a** using a ChiralCel OD-H column. The reaction product was found not to epimerize after 16 h in the presence of catalytic TFA or $Et_3N$.

pot protocol (Table 1). Increasing catalyst loading to 40 mol% gave a 10% increase in yield, and decreasing the loading to 5 mol% gave a 10% decrease in yield of product (with 57% *ee*). Extensive variation of the catalyst's dimethylamino group revealed a very high dependence of product yield and *ee* on the amine substituents, with small changes bringing about significant changes in product profile. Changing the methyl groups to other alkyl or acyl substituents invariably eroded both yield and *ee* (entries 2–7), with only a sulfinyl substituent being partially tolerated (entry 8). These results suggested that a Lewis basic group plays a delicate but important role in the mechanism, most likely in the activation of the nitromethane. Keeping the dimethylamino portion constant and varying the rest of the structure revealed that though there was some sensitivity to changes in this region, a group capable of hydrogen bond donation was required (entry 11). It was found that the simple $C_2$-symmetric ligand **1l** (entry 13), previously only used in a dynamic kinetic resolution,[24,25] gave good results.

The mechanism of the asymmetric aza-Henry reaction was explored with catalyst **1a**. Fewer equivalents of nitromethane or higher dilution gave poorer yields, but broadly uniform *ee*. However, *ee* was much more sensitive than yield to solvent polarity (pentane: 76% yield, 31% *ee*; 1,2-DCE: 81, 64; DMF: 66, 4) implying that enantioinduction is mediated by a hydrogen-bonded assembly. The nature of the catalyst-substrate interaction was not clear, specifically whether enantioinduction was occurring in the reaction between DHIQ itself ("unactivated") or with its *in situ*-formed acylated salt.

The screening conditions had involved mixing all reagents except the acetyl chloride at room temperature followed by a reduction of the temperature to −78 °C, addition of AcCl and three hours of stirring. In fact the reaction gave broadly similar results after being stirred for 5 min only at −78 °C (50% yield, 62% *ee*) or when the whole process was conducted at room temperature (85% yield, 52% *ee*). However if DHIQ was initially mixed with solvent and catalyst, then cooled to −78 °C, followed by addition of nitromethane and base, stirred for 3 h then addition of AcCl and stirred for a further 3 h, no product was formed, implying that −78 °C is too low a temperature for nitromethane addition. If the temperature of both steps was increased to −10 °C, the yield and *ee* were good (84%, 66%, respectively) and this improved procedure was used hereafter. *Crucially when the same experiment was performed but the order of addition was reversed (AcCl first, then $MeNO_2$) no product was formed.* These results show that the catalyst is interacting with DHIQ itself and that a scalemic nitroamine intermediate formed between DHIQ and nitromethane is undergoing acylation. Hence the enantioinduction in this case is *via* the addition of nitromethane to the unfunctionalized imine that is presumably transiently activated in the catalyst-substrate complex. The conclusion that the stereochemistry is set by nitromethane addition to the imine was supported by the following preliminary experiments: (i) the initially formed nitro amine does not undergo cross-over upon addition of an excess of nitro*ethane*, as determined by monitoring the reaction with $^1$H NMR spectroscopy, and (ii) racemic nitro amine (formed *in situ* without catalyst) to which was added

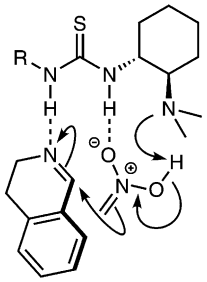


**Figure 1.** Dual activation of DHIQ and nitromethane by bifunctional thiourea catalyst for the asymmetric aza-Henry reaction.

catalyst gave, after quenching with acetyl chloride, racemic **3a** implying that there is no dynamic kinetic resolution of the nitro amine by the catalyst on the time scale of the reaction.

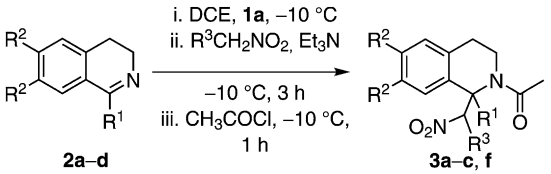
These data suggest the aza-Henry reaction proceeds *via* an unusual mechanism (Figure 1) whereby the catalyst simultaneously activates DHIQ and nitromethane, and the enantioenriched nitro amine is ultimately acylated, presumably off-catalyst, allowing its isolation.

The crucial role of the catalyst dimethylamino moiety is explained if nitromethane exists as its azinic acid tautomer in the catalyst-substrate complex and its deprotonation by the dimethylamino moiety promotes nucleophilic attack; the activation of the imine occurs during the reaction mechanism *via* transient non-covalent interactions.[15] (The role of the exogenous base (triethylamine) is therefore to react with the HCl produced.) Although the *covalent* activation of the imine through acylation might be the more intuitively obvious way of promoting the reaction, such a method would bring the complication of (i) diastereomeric acyliminium ions and (ii) competing electrophilic sites (imine carbon *vs.* carbonyl carbon) between which the catalyst would need to distinguish.[26,27] For the carbon-carbon bond to be formed the DHIQ would need to be oriented as shown to bring the imine carbon into close proximity to the azinic acid carbon, implying the formation of an (*S*)-stereocentre.

The substrate scope of the reaction was explored using four other unactivated cyclic imine substrates (Table 2): 6,7-dimethoxy-3,4-dihydroisoquinoline (**2b**), 1-phenyl-3,4-dihydroisoquinoline (**2c**), 1-methyl-3,4-dihydroisoquinoline (**2d**) and isoquinoline (**2e**).

The 6,7-dimethoxy-DHIQ afforded the product in good yield with relatively low (and reversed) enantioselectivity (entry 2). The substitution on C-1 has a significant impact on the reaction outcome. The 1-phenyl derivative gave a trace amount of product (entry 3) whereas substrate having $CH_3$ at the C-1 position did not give the nitromethane addition product but instead generated the enamide resulting from

**Table 2.** Substrate scope of the reaction.




| Entry | 2 | $R^1$ | $R^2$ | $R^3$ | 3 | Yield[a] [%] | *ee* [%] |
|---|---|---|---|---|---|---|---|
| 1 | **a** | H | H | H | **a** | 84 | 66 |
| 2 | **b** | H | $OCH_3$ | H | **b** | 81 | –49 |
| 3 | **c** | Ph | H | H | **c** | trace | nd[c] |
| 4 | **d** | $CH_3$ | H | H | – | – | – |
| 5 | **a** | H | H | $CH_3$ | **f** | 58 | *dr*[b] |
| 6 | **e** | isoquinoline | | | – | sm[c] | – |

[a] Isolated yield.
[b] DS1:DS2 = 1:0.8, DS1 = 44:56 (racemic reaction); 48:52 (catalytic reaction). DS2 = 46:54 (racemic reaction); 48:52 (catalytic reaction).
[c] nd = not determined; sm = starting material.

elimination of HCl from acylated **2d** (SI-9, entry 4). Isoquinoline did not show any reaction with $MeNO_2$ and only starting material was recovered from the reaction (entry 6). When nitromethane was replaced with nitroethane, the yield dropped giving the product (**3f**) diastereomers in a 1:0.8 ratio but as racemates (entry 5).

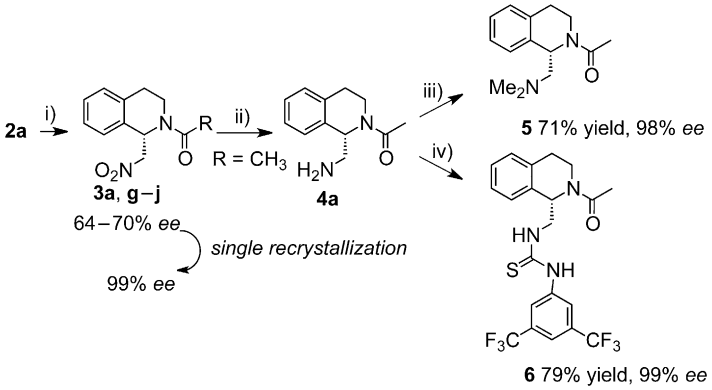
Remarkably the *ee* for compound **3a** increased from 66% to 99% after a single recrystallization from ethyl acetate. The scope of the process was demonstrated through the successful use of four other acylating agents. In each case the scalemic initially-formed compound (**3a**, **g**–**j**) could be obtained enantiopure after one crystallization (Table 3). The *ee* of the dimethoxy derivative increased to 99% after the second recrystallization. Single crystal X-ray diffraction analysis of compounds **3a** and **3g** confirmed the anticipated (*S*)-configuration (see Supporting Information). The relative stereochemistry for the major diastereomer of **3f** (also determined by X-ray crystallography, see Supporting Information) was found to be *syn*, that is, (*R*,*R*) and (*S*,*S*).

The enantiopure beta-nitro amines are entry points to a range of structures based on chiral vicinal diamines. Reduction of **3a** to the corresponding amine could be achieved in 85% yield with Raney nickel under mild conditions with no loss of *ee*. The enantiopure amine **4a** could be further functionalized by alkylation (to give **5**) or conversion to the thiourea **6**, again with no loss of *ee* in either case. These are novel chiral diamine motifs that are interesting prototypes for new classes of asymmetric catalyst ligands currently under investigation in our laboratory.

In summary, we have reported the first catalytic, asymmetric aza-Henry reaction on an unactivated cyclic imine. The reaction successfully operates open

**Table 3.** Recrystallization of aza-Henry reaction products and subsequent modification.[a]




| Series | R | Initially formed **3** | | Recrystallized **3** | |
|---|---|---|---|---|---|
| | | Yield[b] [%] | *ee* [%] | Yield[c] [%] | *ee* [%] |
| **a** | $CH_3$ | 84 | 66 | 55 | 99 |
| **g** | $CH_2Cl$ | 92 | 64 | 58 | 99 |
| **h** | Ph | 76 | 64 | 48 | 99 |
| **i** | *p*-Br, Ph | 69 | 70 | 34 | 99 |
| **j** | $OCH_2CH_3$ | 89 | 64 | 55 | 99 |
| **b**[d] | $CH_3$ | 81 | 49 | 25[e] | −99[e] |

[a] Reaction conditions: i) a. DCE, catalyst **1a** (20 mol%), −10 °C, 10 min, b. $MeNO_2$, $Et_3N$ at −10 °C, 3 h, c. RCOCl at −10 °C, 1 h, ii) $H_2$ (balloon), Raney Ni, $NH_3$/MeOH (1:10), room temperataure, 3 h. iii) HCHO (aqueous), $NaBH(OAc)_3$, DCE, room temperature, 2 h. iv) 3,5-Bis(trifluoromethyl)phenyl isothiocyanate, $Et_3N$, DCM, 0 °C, 1 h.
[b] Isolated yield.
[c] Yield based on the starting material.
[d] 6,7-Dimethoxy-3,4-dihydroisoquinoline.
[e] Yield and *ee* after second recrystallization.

to the air and using nitromethane that has not been dried. The reaction does not require a strong base for the generation of a nitronate. The nitro amine products may be crystallized to enantiopurity and used in the synthesis of new chiral amine-derived scaffolds.

## Experimental Section

### General Procedure for the Synthesis and Crystallization of Enantiopure Aza-Henry Products

***Synthesis and crystallization of 3a:*** To a solution of **2a** (200 mg, 1.50 mmol) in DCE (5.0 mL) was added catalyst **1a** (124 mg, 0.30 mmol) at room temperature. The reaction flask was capped with a rubber septum and was cooled to −10 °C and the mixture stirred for 10 min. Nitromethane (725 μL, 13.5 mmol) and $Et_3N$ (310 μL, 2.20 mmol) were added and the reaction mixture was stirred for 3 h at −10 °C. Acetyl chloride (320 μL, 4.50 mmol) was added and stirring was continued for 1 hour at −10 °C. Solvents were removed under vacuum and the residue was purified by flash chromatography on silica gel (EtOAc:hexane = 1:1) to give **3a** as a colourless solid; yield: 302 mg (84%, 66% *ee*), which was recrystallized from EtOAc (approx. 6 mL) at room temperature to give enantiopure **3a** as colourless tablet-shaped crystals; yield: 196 mg (55%, 99% *ee*).

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