

An enantioselective tandem reduction/nitro-Mannich reaction of nitroalkenes using a simple thiourea organocatalyst†

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There is a continual need for ever more effective and operationally simpler methods for the asymmetric synthesis of nitrogen containing molecules. We report here a generally efficient synthesis of stereochemically defined β -nitroamine building blocks which, through the combination of two catalytic transformations into one tandem process, results in the use of a simpler asymmetric catalyst, less reaction materials, shorter reaction times, circumvents the need for moisture sensitive reaction partners and leads to a wider substrate scope. Using *para*-methoxy-phenyl (PMP) protected imines, a Hantzsch ester as hydride source and a simple and economic thiourea organocatalyst, we have promoted the nitro-Mannich reaction with a nitroalkene to form *anti*- β -nitroamines. After protection as their trifluoroacetamides the products can be isolated in good yields (32–83%), high diastereomeric ratios (90 : 10 to >95 : 5) and excellent enantioselectivity (73–99% ee).

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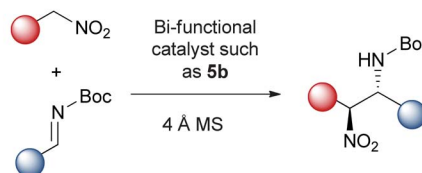
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Introduction

Functional groups containing nitrogen are present in 75% of all drug molecules, in every major drug class and in a wide variety of biologically active natural products.¹ The β -nitroamine functionality has emerged as a privileged building block due to its complimentary synthetic flexibility available from the two different nitrogen atom oxidation states. As such it has been applied in the synthesis of many nitrogen containing functional groups including α -amino carbonyls,² 1,2-diamines,³ peptidomimetics,⁴ natural products⁵ and many heterocyclic small molecules⁶ of importance to drug discovery. This stereodefined bifunctional building block is most commonly made by an enantioselective nitro-Mannich (or aza-Henry) reaction (Scheme 1). Enantioselective reactions have been controlled by asymmetric metal centered Lewis acids; chiral hydrogen bond donors, in particular by the use of asymmetric thiourea organocatalysts; chiral Brønsted acids; phase transfer catalysts and Brønsted base catalysts.⁷ However, many enantioselective nitro-Mannich reactions largely suffer from several limitations including a requisite for a large excess of nitroalkane and/or long reaction times;⁸ limited availability of complex nitroalkanes; and in the majority of cases the use of moisture sensitive *N*-Boc imines (Scheme 1a). The demand for making

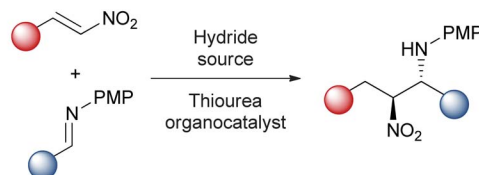
complex molecular architectures with high operational efficiencies has led to the development of many complex asymmetric catalysts.⁹ One way of simplifying these procedures is to combine catalytic reactions in a tandem process.¹⁰ We report a

a) typical thiourea catalysed nitro-Mannich reaction



- Long reaction times and/or
- Large excess of nitroalkane due to slow rates of deprotonation
- Limited commercial availability of complex nitroalkanes
- Use of moisture sensitive *N*-Boc imines

b) reductive nitro-Mannich reaction, this work



- Expedient synthesis of β -nitroamines
- Nitroalkene partner easily accessed *via* Henry condensation
- Faster formation of reactive nitronate species than *via* deprotonation?
- Potential to build 3 contiguous stereocentres

Scheme 1 Comparison of previous work.

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† Electronic supplementary information (ESI) available: Method of determining absolute stereochemistry, detailed catalyst screen, full experimental details, ¹H and ¹³C NMR spectra for all new compounds and HPLC data. See DOI: 10.1039/c3sc50613d

solution to these problems using an asymmetric tandem reductive nitro-Mannich strategy, with nitroalkenes and N-PMP imines, catalysed by a simple thiourea organocatalyst (Scheme 1b).¹¹ The combination of these two catalytic transformations into one tandem process led to the use of a simpler asymmetric catalyst, less equivalents of nitroalkene and reductant, shorter reaction times and circumvented the need for moisture sensitive N-Boc imines. This concept generally may simplify other catalytic systems and specifically will allow the wider synthesis of this versatile building block.

Results and discussion

Proof of concept and reaction optimisation

Both nitro-Mannich reactions^{12,13} and reductions of nitroalkenes¹⁴ have been shown to be amenable to asymmetric thiourea organocatalysis, so a tandem reaction appeared plausible. Initially, we tested catalyst **5a**, previously shown by Jacobsen to be effective for nitro-Mannich reactions,^{13b} in a tandem reduction/nitro-Mannich reaction with β -nitrostyrene **1a** and Hantzsch ester **4** as hydride source (Table 1). The reaction with N-Boc protected imine failed to give the desired product, instead preferentially reducing N-Boc imine (Table 1, Entry 1). However by switching to the less electrophilic N-PMP protected imine we were able to promote the desired tandem reductive nitro-Mannich reaction. Due to the instability of the β -nitroamine products, an *in situ* trifluoroacetamide protection was performed,¹⁵ and **3** was isolated in 29% yield and in 58% ee after 1 h (Table 1, entry 2). Extended reaction times initially gave an increase in the reaction yield, up to 9 h when β -nitrostyrene **1a** had been fully consumed (Table 1, entry 3). Further ageing of the reaction however gave a decreased yield and lower

enantioselectivity due to retro-addition (Table 1, entry 4). Interestingly, when using ethyl ester substituted Hantzsch ester **4b** only 10% nitroalkene reduction was observed and <5% conversion to desired product **3** (Table 1, entry 5).¹⁶ Before undertaking a catalyst screen, the stoichiometry of the reaction was examined and it was discovered that by employing 2 equivalents each of the nitroalkene and hydride source the reaction was faster and higher yielding with little effect on the enantioselectivity of the reaction (Table 1, entry 6). Increasing the stoichiometry of imine had no effect on the relative rate of reaction (Table 1, entry 7) suggesting that the reduction of the nitroalkene is the rate limiting step. The reaction was also attempted in a stepwise manner where imine **2** was charged after complete reduction of **1** (Table 1, entry 8). This resulted in no formation of desired product **3** prompting us speculate that the two reactions occur in tandem.

Optimisation of asymmetric catalyst

Using these optimised conditions we then screened the reaction with a variety of thiourea organocatalysts (Table 2).¹⁷ Take-moto's catalyst **5b**,¹⁸ failed to reduce nitroalkene **1a** and

Table 1 Optimisation of reductive nitro-Mannich reaction

Entry	PG	R	Rxn time (h)	Yield (%)	dr ^a	ee ^b (%)
1	Boc	CO ₂ ^t Bu	16	<5	—	—
2	PMP	CO ₂ ^t Bu	1	29	95 : 5	58
3	PMP	CO ₂ ^t Bu	9	45	95 : 5	52
4	PMP	CO ₂ ^t Bu	22	23	90 : 10	34
5	PMP	CO ₂ Et	22	<5	—	—
6 ^c	PMP	CO ₂ ^t Bu	2	77	95 : 5	50
7 ^d	PMP	CO ₂ ^t Bu	1	30	95 : 5	57
8 ^e	PMP	CO ₂ ^t Bu	9	<5	—	—

^a Determined by ¹H NMR analysis. ^b Determined by chiral HPLC see ESI. ^c 2 equiv. of **1** and **4a**. ^d 2 equiv. of **2**. ^e Reaction performed using a stepwise addition.

Table 2 Optimisation of asymmetric catalyst^a

<p>5a</p>		<p>5b</p>	
87% yield, 95 : 5 dr, 50% ee		No reaction	
<p>5c</p>		<p>5d</p>	
25% yield, >95 : 5 dr, 86% ee		48% yield, >95 : 5 dr, 90% ee	
<p>5e</p>		<p>5f (S,S)</p>	
36% yield, >20 : 1 dr, -65% ee		37% yield, 95 : 5 dr, 76% ee	
<p>5g</p>		<p>5h</p>	
72% yield, >95 : 5 dr, 90% ee		75% yield, 90 : 10 dr, 90% ee 81% yield, 95 : 5 dr, 90% ee ^b	

^a Reaction of N-PMP imine (0.14 mmol) with **1a** (2 equiv.), **4a** (2 equiv.) and **5** (10 mol%) in toluene (1 mL) at rt for 2 h. ^b Reaction performed at -20 °C over 24 h.



consequently no nitro-Mannich reaction was observed. Using catalyst **5c**, which has been previously used for asymmetric reductions of nitroalkenes,¹⁴ we obtained a high degree of enantioselectivity (86% ee) but in a poor yield (25%, extended reaction times did not lead to an improvement in yield). Toluenesulfonamide catalyst **5d** gave the desired product with excellent enantioselectivity (90% ee) and a moderate yield of 48% (extended reaction times led to a maximum yield of 75% with an 88% ee). To explore which chiral group was responsible for stereoselection, we screened catalyst **5e**, which gave the opposite enantiomer to that obtained with **5d** with 64% ee; and diastereomeric catalyst **5f**, which gave the same enantiomer as that obtained with **5d**, albeit with a slightly reduced yield and enantioselectivity (37%, 76% ee). These two results suggest that the diaminocyclohexane group is not responsible for the high degree of stereoselectivity. Due to the relatively high cost of unnatural amino acid *L*-tert-leucine, we also synthesised catalyst **5g** using the significantly cheaper *L*-valine and were surprised to observe the same high levels of enantioselectivity (90% ee). Combining these results we replaced the diaminocyclohexane moiety with an aryl group to give catalyst **5h** which achieved a high level of enantioinduction (90% ee) and yield (75%). With catalyst **5h** showing good potential we conducted a solvent screen that confirmed toluene as the best choice (see ESI†). Further investigation of the reaction in toluene at rt showed complete consumption of the imine after 30 min and immediate protection enabled isolation of **3** in 74% yield with an impressive 94% ee. This result suggested that stereoselectivity was probably being eroded at rt due to the reversibility of the nitro-Mannich reaction. In order to retard the retro-addition reaction we performed the reaction at lower temperatures (see ESI†). At -20°C the desired product was isolated in excellent yield and stereoselectivity (81% yield, >95 : 5 dr and 98% ee) after 20 h. Prolonged reaction at -20°C did not lead to a decrease in enantioselectivity suggesting no retro-addition occurs (see ESI†).

Reaction optimisation with respect to imines 2

With these optimised conditions we examined the scope of the reaction, initially with respect to imines **2** (Table 3). Both electron rich and electron poor aromatic imines (Table 3, entries 2–7) gave uniformly high yields and excellent stereoselectivities, although the *ortho*-trifluoromethyl substituted electron deficient imine (Table 3, entry 5) was less enantioselective (80% ee). The crude diastereoselectivities for all the *ortho*-substituted substrates (Table 3, entries 5–7) were lower than that of the purified products. All of the *syn*-diastereoisomers isolated from these analogues were of low enantiopurity which may suggest that there are different transition states in operation for each diastereoisomer. The reaction worked well for heterocyclic imines (Table 3, entries 8–9), but less so for an alkyl ⁿpentyl substituted product **3aj** which was formed in moderate 73% ee (Table 3, entry 10).

The yield of the reaction was also reduced due the instability of the ⁿpentyl substituted imine **2j**, even at -20°C . It was found that the yield was best at rt, where the reaction was rapid,

Table 3 Scope of the enantioselective reductive nitro-Mannich reaction with respect to imines

Entry	R ¹	Product	Yield ^a (%)	dr ^b	ee ^c (%)
1	Ph	3aa	81	>95 : 5 (>95 : 5)	98
2	<i>p</i> -MeOPh	3ab	75	>95 : 5 (>95 : 5)	97
3	<i>o</i> -MeOPh	3ac	83	>95 : 5 (>95 : 5)	99
4	<i>p</i> -F ₃ CPh	3ad	74	90 : 10 (90 : 10)	94
5	<i>o</i> -F ₃ CPh	3ae	66	>95 : 5 (80 : 20)	80 (4)
6	<i>o</i> -MePh	3af	75	>95 : 5 (85 : 15)	90 (34)
7	<i>o</i> -BrPh	3ag	70	>95 : 5 (80 : 20)	92 (10)
8	2-Furyl	3ah	77	90 : 10 (90 : 10)	97
9	2-Pyridyl	3ai	76	>95 : 5 (>95 : 5)	96
10 ^d	ⁿ Pentyl	3aj	59	>95 : 5 (>95 : 5)	73

^a Isolated yield of **3**. ^b dr of isolated **3** calculated by ¹H NMR, parentheses indicate dr of crude product. ^c Determined by chiral HPLC, parenthesis indicate ee of *syn*-diastereomer if isolated. ^d Reaction performed at rt over 1 h.

without any noticeable effect on the enantioselectivity allowing isolation of **3aj** in 59% yield.

Reaction optimisation with respect to nitroalkenes 1

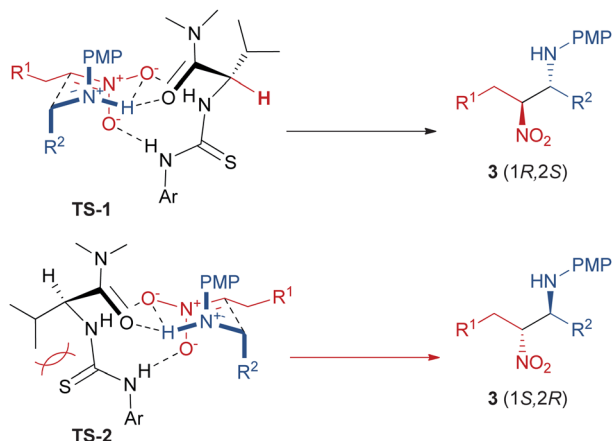
The nitroalkene partner tolerated alkyl substituents, substituted aromatics and heterocyclic analogues exceptionally well giving high yields and excellent stereoselectivity (Table 4, entries 1–7). A decrease in the rate of the reaction was observed

Table 4 Scope of the enantioselective reductive nitro-Mannich reaction with respect to nitroalkenes

Entry	R ¹	Product	Rxn time (h)	Yield ^a (%)	dr ^b	ee ^c (%)
1	ⁿ Pentyl	3ba	20	71	>95 : 5	97
2	Cyclohexyl	3ca	20	75	>95 : 5	95
3	<i>o</i> -BrPh	3da	20	79	>95 : 5	98
4	<i>o</i> -F ₃ CPh	3ea	20	73	>95 : 5	95
5	2-Pyridyl	3fa	28	68	>95 : 5	98
6	<i>o</i> -MePh	3ga	48	70	>95 : 5	98
7	<i>o</i> -MeOPh	3ha	72	64	>95 : 5	98
8	2-Furyl	3ia	240	32	>95 : 5	95

^a Isolated yield of **3**. ^b dr of crude **3** calculated by ¹H NMR, which remained unchanged after purification. ^c Determined by chiral HPLC.





Scheme 2 Origin of enantioselectivity.

when using more electron rich nitroalkenes (Table 4, entries 6–8). This effect was most evident when using 2-furyl nitroalkene **11** which required a reaction time of 10 days to consume all of imine **2a** (Table 4, entry 8). This increased reaction time also led to decreased yields due to competitive reduction of imine **2**. This result also suggests that the reduction is the rate determining step of the reaction.

Mechanistic hypothesis

Our current working hypothesis is that the high enantioselectivity originates from a H-bond stabilised transition state (Scheme 2). This six-membered transition state consists of two H-bonds between the thiourea and nitro group as well as an amide H-bond with the iminium species.

If we assume from the detailed work of Jacobsen on a similar catalyst that the most stable conformation of catalyst **5h** is when the highlighted C–H bond is in the same plane as the large C=S bond,¹⁹ the amide can freely H-bond to the iminium species in a *pseudo* equatorial position (**TS-1**) giving rise to the observed

enantiomer. Conversely, to obtain the opposite enantiomer the *iso*-propyl group would be required to be in the same plane as the C=S bond (**TS-2**). Such a conformation would have a large steric penalty and would as such be unfavorable.

Preliminary investigations into forming three contiguous stereocentres

Pleased with the results using simple nitrostyrene derivatives we wished to examine the potential of this reaction to form nitro-Mannich products containing three contiguous stereocentres. Using nitroalkene **6** and our thiourea catalyst **5h** we were pleasingly able to obtain **7a** in high enantiopurity (84% ee) and excellent diastereoselectivity (95 : 0 : 5 : 0 dr) after 17 h at room temperature, albeit in a low yield of 37% (Table 5, entry 3). Interestingly, the reaction initially favoured formation of the *syn*, *anti*-diastereomer **7b** before converting to **7a**. We are currently unsure as to the mechanism of this interconversion but believe it may be formed *via* a retro addition/nitro-Mannich sequence.²⁰ Further investigations and optimisations of this intriguing reaction are currently underway.

Conclusions

We have developed the first asymmetric tandem reductive nitro-Mannich reaction using a simple thiourea organocatalyst and a Hantzsch ester as hydride source. The reaction uses the simplest thiourea organocatalyst applied to a nitro-Mannich reaction yet and in general does not suffer from the long reaction times or large excess of reagents required of previous reports. The reductive nitro-Mannich strategy provides an opportunity for more diverse substrates and the reaction is tolerant of a variety of different nitroalkenes and imines. To the best of our knowledge this is also the first organocatalysed nitro-Mannich reaction using PMP-imines, which significantly simplifies the experimental conditions of the reaction and should enable wider use in synthesis. We are currently beginning detailed experimental and computational investigations into the origin of the exceptionally high levels of enantioselectivity considering the simplicity of the catalyst.

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Table 5 Preliminary investigations into forming three contiguous stereocentres

Entry	Rxn time (h)	Conv. to 7 ^a (%)	Yield ^b (%)	dr ^c (a : b : c : d)	ee ^d (%)
1	0.5	10	n.d.	10 : 80 : 10 : 0	n.d.
2	2.5	30	n.d.	65 : 5 : 30 : 0	n.d.
3	17	55	37	95 : 0 : 5 : 0	84

^a Calculated by ¹H NMR. ^b Isolated yield of 7. ^c dr of crude 7 calculated by ¹H NMR. ^d Determined by chiral HPLC.



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