Letter

One-Pot Asymmetric Nitro-Mannich/Hydroamination Cascades for the Synthesis of Pyrrolidine Derivatives: Combining Organocatalysis and Gold Catalysis

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One-Pot Asymmetric Nitro-Mannich/Hydroamination Cascades for the Synthesis of Pyrrolidine Derivatives: Combining Organocatalysis and Gold Catalysis.

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ABSTRACT: The highly enantioselective preparation of trisubstituted pyrrolidine derivatives employing a one-pot nitro-Mannich/hydroamination cascade is reported. This cascade approach utilizes an asymmetric bifunctional organocatalytic nitro-Mannich reaction followed by a gold-catalyzed allene hydroamination reaction. The products are afforded in good yields and excellent diastereo- and enantioselectivities.

Pyrrolidine heterocycles are prevalent structures found in a myriad of biologically active molecules and natural products (Figure 1).[1] Due to the abundance of the pyrrolidine motif, research into the synthesis of such an important structural unit continues to be an attractive challenge for the reaction designer.[2]

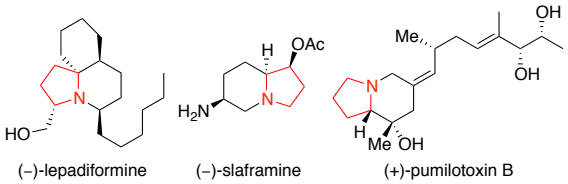
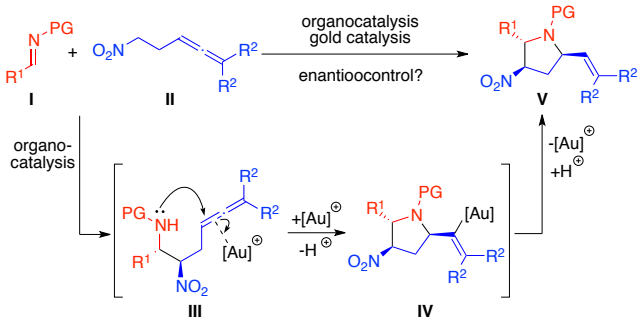


Figure 1. Selection of biologically active natural products containing pyrrolidine motifs.

Recently, cascade reactions have emerged as a powerful tool for the preparation of single and polycyclic systems.[3] Cascade reactions are typically resource efficient and can rapidly build up molecular complexity without the need for isolation of the intermediate compounds. As part of our ongoing research program into cascade reactions using nitro-Mannich[4] and hydroamination[5] reactions, we envisaged that a nitro-Mannich/hydroamination cascade[6] could provide an efficient method to access trisubstituted pyrrolidine derivatives in an enantioselective fashion. Building on our previous diastereoselective pyrrolidine synthesis employing a nitro-Mannich/hydroamination cascade in conjunction with *N*-*p*-toluenesulfonyl protected imines,[6c] we postulated that an effective combination of imine protecting group and organocatalyst would allow this cascade reaction to be conducted in an asymmetric fashion, resulting in a new methodology to produce enantioenriched pyrrolidine heterocycles. Herein we report our findings.

In our proposed concept (Scheme 1), nitroallene **II** would react with a protected imine **I** using an appropriate organocatalyst.[7] The resulting enantioenriched β-nitroamine **III** would then be poised to cyclise via a diastereoselective gold catalysed *5-exo-trig* allene hydroamination reaction.[8] Protodemetallation would then afford the desired enantioenriched pyrrolidine **V** and allow the catalytic cycle to continue.



Scheme 1. Concept of an enantioselective pyrrolidine synthesis using a nitro-Mannich/hydroamination cascade.

Our previous investigation[6c] had utilised *N*-*p*-toluenesulfonyl protected imines for the nitro-Mannich/hydroamination cascade reaction. However, this protecting group is known to give low enantioselectivities in organocatalysed nitro-Mannich reactions,[4a]

making it unsuitable for this study. In addition, *N*-Boc and *N*-phosphinoyl protected substrates did not undergo the allene hydroamination reaction in our previous study.[6c] Therefore, we decided to investigate *N*-Cbz protected imines as a possible solution to our reactivity and stereoselectivity issues.

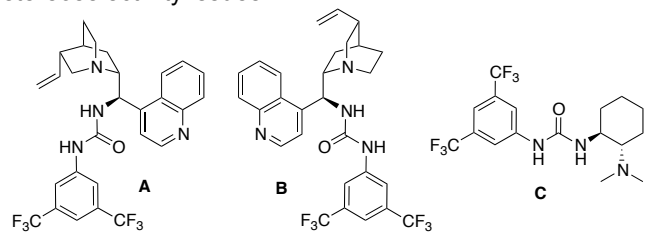
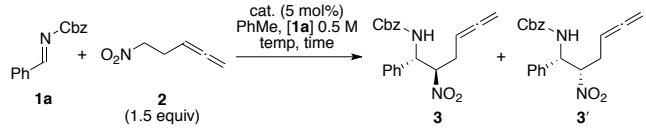


Figure 2. Organocatalysts used in preliminary enantioinduction screen in the nitro-Mannich reaction of *N*-Cbz imine **1a** and nitroallene **2**.

Table 1. Optimisation of the diastereo- and enantioselectivity in the organocatalytic nitro-Mannich reaction of *N*-Cbz imine **1a** and nitroallene **2**.



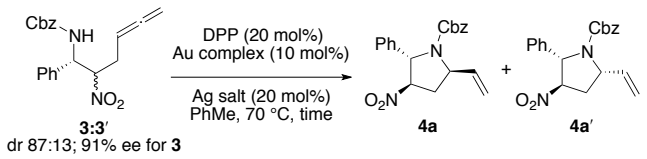
entry[a]	cat.	temp (ºC)	time (h)	yield (%)[b]	dr[c] **3:3′**	ee (%)[d] **3/3′**
1	A	RT	20	59	65:35	55/33[c]
2	C	RT	15	77	75:25	86/75
3	A	–15	72	57	79:21	51/37[c]
4	B	–15	72	59	82:18	58/55
5	C	–15	44	77	87:13	91/77

[a] All reactions were conducted on a 0.10 mmol scale. [b] Isolated yield after purification by flash column chromatography. [c] Determined by HPLC analysis of the purified product. [d] Opposite enantiomers obtained.

Accordingly, we investigated the level of enantioinduction obtained in the nitro-Mannich reaction between *N*-Cbz imine **1a** and nitroallene **2** using organocatalysts **A**, **B**, and **C** (Figure 2).[9] After a concise optimisation study (Table 1), we found that the use of catalyst **C** (5 mol%) at –15 °C and a concentration of 0.5 M resulted in the best diastereo- and enantioselectivity in the formation of β-nitroamine **3** (dr 87:13, 91% ee for the major isomer **3**) as well as the best isolated yield (77%; Table 1, entry 5).

With these results in hand, studies into the hydroamination reaction of the enantioenriched β-nitroamines **3** and **3′** were then conducted (Table 2). Pleasingly, β-nitroamines **3** and **3′** (dr 87:13, 91% ee for the major diastereomer **3**) were successfully cyclised using a catalyst combination of $Au(PPh_3)Cl$ (10 mol%) and $AgSbF_6$ (20 mol%),[10] affording pyrrolidine **4a** in 61% yield and 81:19 crude dr without erosion of the enantioselectivity observed in β-nitroamine **3** (91% ee; Table 2, entry 1).[11] Changing the silver salt to AgOTf and $AgNTf_2$ gave minor increases in the diastereoselectivity of the hydroamination reaction whilst maintaining good yields of pyrrolidine **4a** (Table 2, entries 2 and 3).

Table 2. Cyclisation optimisation of β-nitroamines **3** and **3′**.

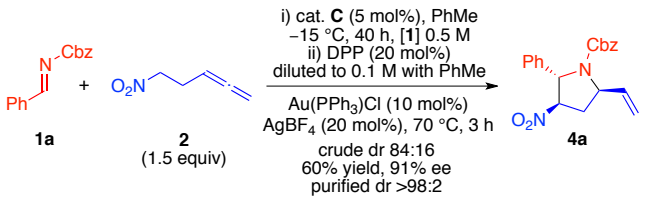


entry[a]	Au complex (10 mol%)	Ag salt (20 mol%)	time (h)	yield (%)[b]	dr[c] **4a:4a′**	ee (%)[d]
1	$Au(PPh_3)Cl$	$AgSbF_6$	2	61	81:19	91
2	$Au(PPh_3)Cl$	AgOTf	2	58	83:17	91
3	$Au(PPh_3)Cl$	$AgNTf_2$	2	65	82:12	91
4	$Au(PPh_3)Cl$	$AgBF_4$	2	69	89:11	91
5	$Au[(PhO)_3P]Cl$	$AgBF_4$	4	54	80:20	91
6	$Au(PtBu_3)Cl$	$AgBF_4$	3	50	83:17	91

[a] All reactions were conducted on a 0.10 mmol scale. [b] Isolated yield of single diastereomer **3** after purification by flash column chromatography on silica gel. [c] Determined by ^1H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis of the purified product; ee of the major diastereomer **4a** is shown, ee of the minor diastereomer **4a′** was not determined. DPP = Diphenylphosphate

Employment of $AgBF_4$ not only gave an improved yield of pyrrolidine **4a** (69%), but the diastereoselectivity of the crude reaction mixture was also improved (dr 89:11; Table 2, entry 4). Changing the ligand of the gold complex to a phosphite, led to a reduced yield of pyrrolidine **4a** and erosion of the diastereoselectivity (Table 2, entry 5).[12]

With both the nitro-Mannich and hydroamination reactions independently optimised, we were confident that combining these two reactions in a sequential cascade procedure would allow for a highly enantioselective pyrrolidine synthesis.[13] Pleasingly, the sequential procedure was successful, affording pyrrolidine **4a** in 60% yield and 91% ee as a single diastereomer after separation of the minor diastereomer by column chromatography. (Scheme 2).[14]

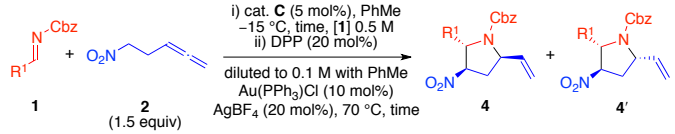


Scheme 2. One-pot asymmetric nitro-Mannich/hydroamination cascade reaction to pyrrolidine **4a**. DPP = Diphenylphosphate

To examine the scope of the developed reaction cascade, a series of substituted *N*-Cbz imines **1** were sub-

jected to our optimised nitro-Mannich/hydroamination conditions (Table 3). Pleasingly, the cascade reaction was shown to tolerate variations in the substituents present on the aromatic ring of the *N*-Cbz imines. The electron-poor halogen (fluoro, chloro and bromo) substituted imines all afforded the desired enantioenriched pyrrolidines **4b-4f** in moderate to good yields (36-58%). The diastereoselectivity observed in the crude reaction mixtures were generally good (dr 78:22-85:15) with the major isomer being isolated as a single diastereomer after purification with excellent enantioselectivities in all cases (90-96% ee).

Table 3. Scope of the enantioselective nitro-Mannich/hydroamination cascade for the enantioselective synthesis of pyrrolidines **4** and **4′**.



entry[a] (**4:4′**)	R^1	i) time (h)	ii) time (h)	crude dr[b] **4:4′**	yield (%)[c]	dr[d] **4:4′**	ee (%)[e]
1 (**a**)	Ph	40	3	84:16	60	92:8	90
2 (**b**)	*o*-ClC_6H_4	48	3	85:15	52	>98:2	90
3[f] (**c**)	*p*-ClC_6H_4	24	2	79:21	36	>98:2	93
4(**d**)	*m*-FC_6H_4	48	4	78:22	58	>98:2	95
5[f] (**e**)	*p*-FC_6H_4	40	2	84:16	50	>98:2	94
6[f] (**f**)	*m*-BrC_6H_4	40	3	84:16	54	>98:2	96
7 (**g**)	*o*-MeC_6H_4	40	2	82:18	66	>98:2	91
8[f] (**h**)	*p*-MeC_6H_4	40	3	81:19	53	>98:2	91
9 (**i**)	*o*-$MeOC_6H_4$	54	3	76:24	39	>98:2	85
10[f] (**j**)	*m*-$MeOC_6H_4$	40	2	84:16	64	>98:2	92
11 (**k**)	*m*,*p*-$(MeO)_2C_6H_3$	40	2	85:15[g]	67	93:7[h]	92
12[f] (**l**)	*m*,*p*-$(OCH_2O)C_6H_3$	40	2	86:14	67	96:4	91
13 (**m**)	2-thienyl	48	14	87:13	32	88:12	85

[a] All reactions were conducted on a 0.20 mmol scale. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Yield after purification by flash column chromatography on silica gel. [d] Determined by ^{1}H NMR analysis of the purified product; dr >98:2 minor isomer was **4′** not visible by ^{1}H NMR analysis. [e] Determined by HPLC analysis of the purified product. [f] Minor diastereomer **4′** isolated in this example; see ESI for details. [g] Approximately 8% of a third diastereomer of unknown configuration was visible in the crude ^{1}H NMR spectrum. [h] The minor diastereomer refers to that of unknown configuration, see footnote g. DPP = Diphenylphosphate

In the preparation of compounds **4c**, **4e** and **4f**, the minor isomers were also isolated after purification by column chromatography on silica gel with excellent enantioselectivities (93-94% ee). Methoxy substituted aryl groups were also found to be suitable substrates for the cascade reaction. The *ortho*-methoxy substituted aryl pyrrolidine **4i** did suffer from a diminished yield and enantioenrichment (39% yield, 85% ee), but all of the other pyrrolidines bearing methoxy groups were afforded with good yields (64-67%) and enantioselectivities (91-92% ee). The minor diastereomers **4j′** and **4l′** were also isolated from these reactions. The electron-rich 2-thienyl substituted pyrrolidine **4m** was pleasingly furnished by the cascade reaction, although it was obtained in only 32% yield and 85% ee.

To prove the absolute configuration of the prepared pyrrolidines **4**, we obtained a single crystal of pyrrolidine **4k** for X-ray diffraction analysis by crystallisation from CH_2Cl_2. The X-ray diffraction data showed that pyrrolidine **4k** contained a (2*S*,3*R*,5*R*) configuration (Figure 3).[15] All other major pyrrolidine diastereomers **4** were assigned by analogy.

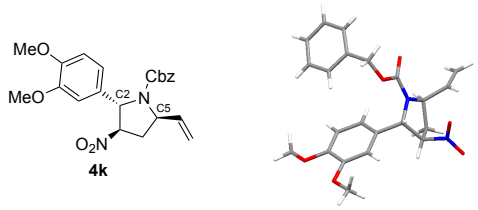
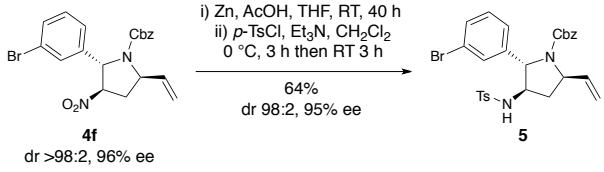


Figure 3. X-Ray crystal structure representation of pyrrolidine **4k**.

The relative configuration of the minor pyrrolidines **4′** was determined using NOESY analysis of pyrrolidine **4h′**.[16] In this experiment the *cis* configuration of the protons in the C2-C5 positions was confirmed, see ESI for details. All other minor pyrrolidine diastereomers **4′** were assigned by analogy.

To demonstrate that the enantioenrichment of the synthesised products was retained in subsequent reactions, pyrrolidine **4f** was transformed into the sulfonamide containing pyrrolidine **5** using a two-step procedure (Scheme 3). Firstly, reduction of the nitro group using zinc powder and acetic acid in THF at RT proceeded smoothly to furnish the amine which was then reacted with *p*-TsCl in the presence of Et_3N to afford pyrrolidine **5** in excellent enantioselectivity (dr 98:2, 95% ee).



Scheme 3. Nitro group reduction of pyrrolidine **4f**.

In summary, we have developed an enantioselective synthesis of substituted pyrrolidines using a nitro-Mannich/hydroamination cascade methodology. The combination of bifunctional organocatalysis and gold catalysis used in conjunction with *N*-Cbz imines afforded pyrrolidines **4** in moderate to good yields (32-67%) with excellent enantioselectivities (85-96% ee). This methodology will allow new highly substituted pyrrolidine based architectures to be prepared for library generation and target synthesis.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) Single-crystal X-ray diffraction data were collected at 150K with an Oxford Diffraction SuperNova diffractometer and processed with CrysAlisPro as per the Supporting Information (CIF). The structure was solved with SIR92[17] and refined with CRYSTALS[18] including the Flack χ parameter[19] which refined to 0.04(11). Full crystallographic data (in CIF format) are available as Supporting Information and have been deposited with the Cambridge Crystallographic Data Centre (reference code 975402).

(16) The configuration of **4h′** at the C2-C3 positions was assigned as *trans* because the proton in the C2 position showed such a small coupling constant with the proton in the C3 ($^3J_{H,H} \approx 90°$), see: (a) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870–2871. (b) Minch, M. J. *Concept Magnetic Res.* **1994**, *6*, 41–56.

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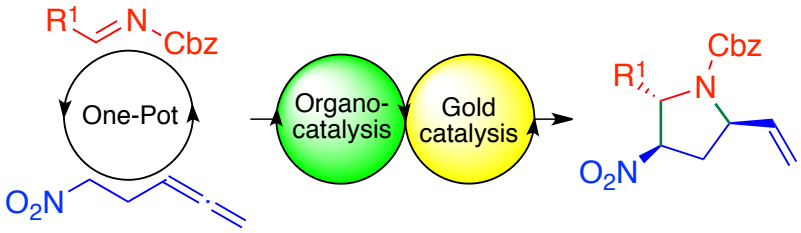
The highly enantioselective preparation of trisubstituted pyrrolidine derivatives employing a one-pot nitro-Mannich/hydroamination cascade is reported. This cascade approach utilizes an asymmetric bifunctional organo-catalytic nitro-Mannich reaction followed by a gold-catalyzed allene hydroamination reaction. The products are afforded in good yields and excellent diastereo- and enantioselectivities.



13 examples
up to 67% yield, 87:13 dr and 96% ee