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# One-Pot Catalytic Enantioselective Synthesis of Tetrahydropyridines via a Nitro-Mannich/Hydroamination Cascade

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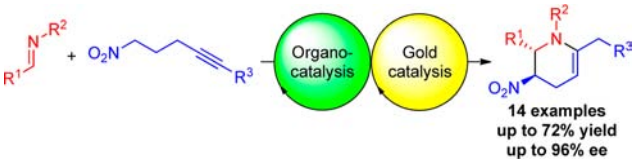
## ABSTRACT




**The highly enantioselective preparation of synthetically useful tetrahydropyridine derivatives employing a one-pot nitro-Mannich/hydroamination cascade is reported. This approach utilizes an asymmetric organocatalytic nitro-Mannich reaction followed by a gold-catalyzed alkyne hydroamination/isomerization sequence that yields the desired tetrahydropyridines in good yields and high diastereo- and enantioselectivities.**

Nitrogen-containing heterocycles such as pyrroles, piperidines, and pyrrolidines are found in a wide variety of biologically active natural products and pharmaceuticals.[1] Due to the abundance of these chemical motifs, improved resource efficient methods for their synthesis remains an important challenge for the reaction designer. Some of the most attractive methods in recent years for the construction of single and polycyclic systems have employed reaction cascades.[2] These multi-reaction sequences are able to efficiently unite readily available starting materials and rapidly build up molecular complexity in the products, without the need for laborious workup and purification procedures of the intermediate compounds. To this end, we recently reported a cascade synthesis of substituted pyrroles via a nitro-Mannich/hydroamination cascade[3] of 4-nitrobut-1-yne.[3a] This reaction cascade utilized a combination of base and gold catalysis to furnish the desired pyrrole products after an isomerization/nitro group elimination sequence. To further advance this work, we postulated that the union of a one-carbon homologue of the nitroalkyne starting material with *N*-protected aldimines promoted by an appropriate catalyst combination could allow rapid access to synthetically useful tetrahydropyridine[4] motifs with high stereocontrol. Herein, we report our findings.

In our proposed concept (Scheme 1), we envisaged that nitro alkyne **II** would undergo an enantioselective nitro-Mannich[5] reaction with a suitably protected aldimine **I**

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(1) For leading references on nitrogen-containing biologically active compounds, see: (a) O'Hagen, D. *Modern Alkaloids: Structure, Isolation, Synthesis and Biology*; Wiley-VCH: Weinheim, Germany, 2007. (b) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139–165 and earlier articles in this series.

(2) For recent reviews of reaction cascades, see: (a) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993–3009. (b) Grondal1, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167–178.

(3) (a) Barber, D. M.; Sanganee, H.; Dixon, D. J. *Chem. Commun.* **2011**, *47*, 4379–4381. For recent examples of one-pot cascades using nitro-Mannich reactions, see: (b) Jakubec, P.; Helliwell, M.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 4267–4270. (c) Xie, J.; Yoshida, K.; Takasu, K.; Takemoto, Y. *Tetrahedron Lett.* **2008**, *49*, 6910–6913. (d) Pelletier, S. M.-C.; Ray, P. C.; Dixon, D. J. *Org. Lett.* **2009**, *11*, 4512–4515. (e) Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 16632–16633. (f) Kyle, A. F.; Jakubec, P.; Cockfield, D. M.; Cleator, E.; Skidmore, J.; Dixon, D. J. *Chem. Commun.* **2011**, *47*, 10037–10039. (g) Pelletier, S. M.-C.; Ray, P. C.; Dixon, D. J. *Org. Lett.* **2011**, *13*, 6406–6409. (h) Jakubec, P.; Kyle, A. F.; Calleja, J.; Dixon, D. J. *Tetrahedron Lett.* **2011**, *52*, 6094–6097. (i) Jakubec, P.; Cockfield, D. M.; Helliwell, M.; Raftery, J.; Dixon, D. J. *Beilstein J. Org. Chem.* **2012**, *8*, 567–578.

(4) For recent examples of tetrahydropyridine synthesis, see: (a) Rueping, M.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 5836–5838. (b) Guo, H.; Xu, Q.; Kwon, O. *J. Am. Chem. Soc.* **2009**, *131*, 6318–6319. (c) Jarvis, S. B. D.; Charette, A. B. *Org. Lett.* **2011**, *13*, 3830–3833. (d) Duttwyler, S.; Lu, C.; Rheingold, A. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 4064–4067.

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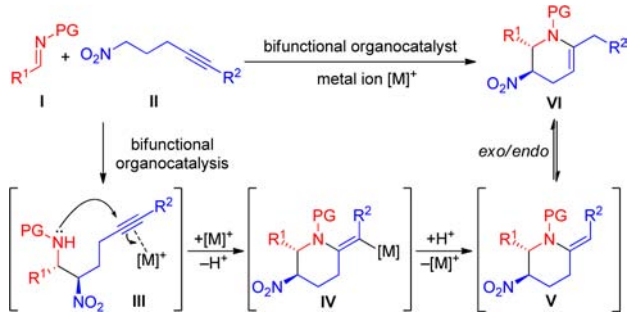
**Scheme 1.** Proposed Enantioselective Synthesis of Tetrahydropyridines Using a Nitro-Mannich/Hydroamination Cascade




under the control of a bifunctional organocatalyst.[6] The resulting $\beta$-nitroamine **III** would then be poised to cyclize via a hydroamination[7] reaction using an appropriate metal catalyst to furnish piperidine **V** after protodemetalation. Subsequent *exo*/*endo* isomerization of the alkene[8] would lead to tetrahydropyridine **VI**. In contrast to our previous study,[3a] an elimination of HONO was not anticipated and accordingly cascade product **VI** was expected to retain the contiguous stereocenters created in the initial nitro-Mannich reaction.

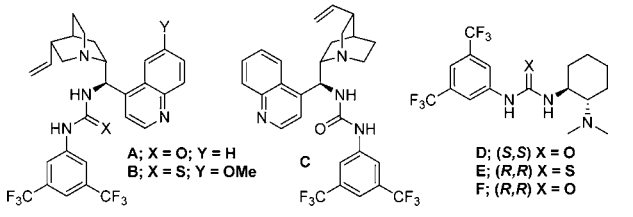
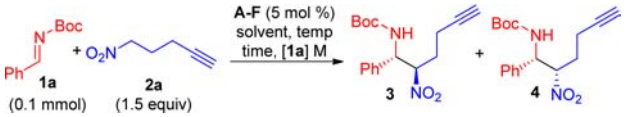



**Figure 1.** Bifunctional organocatalysts screened in the nitro-Mannich reaction of aldimine **1a** and nitro-alkyne **2a** (Table 1).

Accordingly a variety of bifunctional organocatalysts introduced by us and others[9] (Figure 1) were screened in the reaction of *N*-Boc-protected aldimine **1a** and nitro-alkyne **2a** to investigate the diastereo- and enantioselectivity of the nitro-Mannich reaction (Table 1). Various conditions including solvent, temperature, and concentration were explored (for full optimization studies, see Table S1 in the Supporting Information (SI)). Pleasingly, using Takemoto's catalyst **D**[9e−g] in toluene at −15 °C we were able to synthesize $\beta$-nitroamines **3** and **4** in good yield (87%) and diastereoselectivity (87:13), while also obtaining excellent enantioselectivity (92%) for the major diastereomer **3** (Table 1, entry 6).

**Table 1.** Catalyst Optimization Studies in the Reaction of Aldimine **1a** and Nitro-alkyne **2a**




| entry | solvent | time/h | temp/°C | [**1a**] M | cat. | yield (%)[a] | dr **3**:**4**[b] | *ee* **3** / **4** (%)[b] |
|---|---|---|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 48 | rt | 0.1 | **A** | 61 | 70:30 | 62 / 56[c] |
| 2 | PhMe | 48 | rt | 0.1 | **A** | 84 | 66:34 | 71 / 68[c] |
| 3 | PhMe | 48 | rt | 0.1 | **B** | 75 | 67:33 | 66 / 42[c] |
| 4 | PhMe | 48 | rt | 0.1 | **C** | 85 | 65:35 | 60 / 63[d] |
| 5 | PhMe | 24 | rt | 0.1 | **D** | 89 | 66:34 | 69 / 67[d] |
| 6 | PhMe | 24 | −15 | 0.5 | **D** | 87 | 87:13 | 92 / 82[d] |
| 7 | PhMe | 24 | −15 | 0.5 | **E** | 56 | 82:18 | 91 / 68[c] |
| 8 | PhMe | 24 | −15 | 0.5 | **F** | 83 | 86:14 | 93 / 82[c] |

[a] Isolated yield after flash column chromatography. [b] Determined by HPLC analysis of the purified product. [c] (2*R*,3*S*)-**3′** and (2*R*,3*R*)-**4′** obtained. [d] (2*S*,3*R*)-**3** and (2*S*,3*S*)-**4** obtained.

With high enantioselectivity achieved in the nitro-Mannich step using catalyst **D**, our attention then turned to

(5) For a recent review of the nitro-Mannich reaction, see: (a) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626–2704. For selected examples of enantioselective nitro-Mannich reactions, see: (b) Wang, C.-J.; Dong, X.-Q.; Zhang, Z.-H.; Xue, Z.-Y.; Teng, H.-L. *J. Am. Chem. Soc.* **2008**, *130*, 8606–8607. (c) Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 4925–4934. (d) Anderson, J. C.; Stepney, C. J.; Mills, M. R.; Horsfall, L. R.; Blake, A. J.; Lewis, W. *J. Org. Chem.* **2011**, *76*, 1961–1971. (e) Wei, Y.; He, W.; Liu, Y.; Liu, P.; Zhang, S. *Org. Lett.* **2012**, *14*, 704–707.

(6) For selected reviews of bifunctional organocatalysis, see: (a) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713–5743. (b) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638–4660. (c) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138–6171. (d) Giacalone, F.; Gruttadauria, M.; Agrigento, P.; Noto, R. *Chem. Soc. Rev.* **2012**, *41*, 2406–2447.

(7) For selected reviews of hydroamination reactions, see: (a) Aillaud, I.; Collin, J.; Hannedouche, J.; Schulz, E. *Dalton Trans.* **2007**, 5105–5118. (b) Hartwig, J. F. *Nature* **2008**, *455*, 314–322. For selected examples of alkyne hydroaminations in reaction cascades, see: (c) Wang, H.-F.; Yang, T.; Xu, P.-F.; Dixon, D. J. *Chem. Commun.* **2009**, 3916–3918. (d) Ackermann, L.; Barfüsser, S.; Potukuchia, H. K. *Adv. Synth. Catal.* **2009**, *351*, 1064–1072. (e) Patil, N. T.; Mutyala, A. K.; Lakshmi, P. G. V. V.; Gajula, B.; Sridhar, B.; Pottireddygari, G. R.; Rao, T. P. *J. Org. Chem.* **2010**, *75*, 5963–5975.

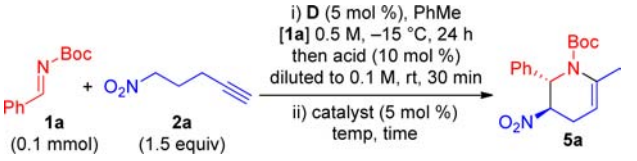
(8) For examples of gold catalyzed alkene isomerization, see: (a) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858–10859. (b) Ito, H.; Harada, T.; Ohmiya, H.; Sawamu, M. *Beilstein J. Org. Chem.* **2011**, *7*, 951–959.

(9) For seminal work using cinchonine and cinchonidine derived bifunctional organocatalysts, see: (a) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367–6370. (b) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967–1969. (c) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481–4483. (d) Li, B.; Jiang, L.; Liu, M.; Chen, Y.; Ding, L.; Wu, Y. *Synlett* **2005**, 603–606. For seminal work using Takemoto's catalyst, including enantioselective nitro-Mannich reactions, see: (e) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673. (f) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625–627. (g) Xu, X.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem.—Eur. J.* **2006**, *12*, 466–476.

(10) For recent reviews of gold catalysis, see: (a) Shapiro, N.; Toste, F. D. *Synlett* **2010**, 675–691. (b) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657–1712. (c) Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2012**, *41*, 2448–2462.

(11) For a recent review of one-pot reactions using organocatalysis and gold catalysis, see: (a) Loh, C. C. J.; Enders, D. *Chem.—Eur. J.* **2012**, *18*, 10212–10225. For selected examples of one-pot reactions using organocatalysis and gold catalysis combined with an acid additive, see: (b) Belot, S.; Vogt, K. A.; Besnard, C.; Krause, N.; Alexakis, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 8923–8926. (c) Jensen, K. L.; Franke, P. T.; Arróniz, C.; Kobbelgaard, S.; Jørgensen, K. A. *Chem.—Eur. J.* **2010**, *16*, 1750–1753. (d) Monge, D.; Jensen, K. J.; Franke, P. T.; Lykke; Jørgensen, K. A. *Chem.—Eur. J.* **2010**, *16*, 9478–9484. (e) Loh, C. C. J.; Badorrek, J.; Raabe, G.; Enders, D. *Chem.—Eur. J.* **2011**, *17*, 13409–13414.

**Table 2.** One-Pot Optimization Studies between Aldimine **1a** and Nitro-alkyne **2a** Using Organocatalysis and Gold Catalysis




| entry | acid | catalyst | (ii) time /h | (ii) temp/ °C | dr[a] | yield (%)[b] | dr[c] | ee (%)[d] |
|---|---|---|---|---|---|---|---|---|
| 1 | 4-nitrophenol | Au(**L1**)$SbF_6$ | 8 | 60 | 84:16 | 11 | 85:15 | 88 |
| 2 | benzoic acid | Au(**L1**)$SbF_6$ | 8 | 60 | 90:10 | 9 | 99:1 | 92 |
| 3 | DPP | Au(**L1**)$SbF_6$ | 6 | 60 | 94:6 | 65 | 99:1 | 93 |
| 4 | *p*-TsOH | Au(**L1**)$SbF_6$ | 3 | 60 | 95:5 | 53 | 99:1 | 93 |
| 5 | DPP | Au(**L2**)Cl[e] | 8 | 60 | 94:6 | 50 | 98:2 | 92 |
| 6 | DPP | Au[$P(OPh)_3$]Cl[f] | 3 | 60 | 92:8 | 33 | 99:1 | 92 |
| 7 | DPP[g] | Au(**L1**)$SbF_6$ | 6 | 60 | 93:7 | 42 | 99:1 | 93 |
| 8 | DPP | Au(**L1**)$SbF_6$ | 24 | rt | 95:5 | 55 | 99:1 | 92 |
| 9 | DPP | Au(**L1**)$SbF_6$ | 8 | 40 | 95:5 | 58 | 99:1 | 91 |
| 10 | DPP | Au(**L1**)$SbF_6$ | 6 | 100 | 91:9 | 55 | 95:5 | 91 |
| 11[h] | DPP | — | 24 | 60 | — | — | — | — |
| 12[h] | — | Au(**L1**)$SbF_6$ | 24 | 60 | — | — | — | — |

[a] Determined by $^1$H NMR analysis of the crude reaction mixture. [b] Isolated yield after flash column chromatography. [c] dr of the purified product determined by HPLC analysis. [d] *ee* of the major diastereomer determined by HPLC analysis. [e] AgOTf (10 mol %). [f] $AgSbF_6$ (10 mol %). [g] DPP (6 mol %). [h] No reaction observed. DPP = Diphenylphosphate; Au(**L1**)$SbF_6$ (Echavarren's catalyst) = (Acetonitrile) [(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate; **L2** = [$P(^tBu)_2$(*o*-biphenyl)].

the development of a one-pot cascade to access the desired tetrahydropyridines. Our previous study[3a] demonstrated that Au[10] salts can very efficiently activate the alkyne functionality toward intramolecular hydroamination reactions. However, due to the known incompatibility of Au(I) catalysts and bifunctional organocatalysts,[11] we adopted the tactic of adding a Brønsted acid to quench the basic *N*-atom of the bifunctional catalyst prior to addition of the Au salt. Our initial investigation used Echavarren's catalyst[12] (5 mol %) with 4-nitrophenol (10 mol %) as the quenching additive (Table 2, entry 1). Pleasingly, the desired tetrahydropyridine **5a** was afforded as a 85:15 mixture of diastereomers in 88% *ee* (for the major diastereomer) after 8 h at 60 °C, albeit with low yield (11%).[13] Further optimization found that addition of diphenylphosphate (10 mol %) prior to addition of the Au catalyst was optimal for the reaction cascade and afforded the desired product in high diastereoselectivity.[14] Purification by silica gel chromatography afforded **5a** as a single diastereomer[15] in 65% yield and 93% *ee* after 6 h at 60 °C (Table 2, entry 3). The use of triflate as the Au counterion resulted in a reduction of the reaction efficiency; **5a** was isolated in 50% yield (Table 2, entry 5). Decreasing the temperature of the hydroamination reaction to rt and 40 °C (Table 2, entries 8 and 9 respectively), led to longer reaction times and slightly impaired yields. When the reaction temperature was increased to 100 °C (Table 2, entry 10) the yield (55%) and diastereoselectivity (crude dr 91:9, purified dr 95:5) decreased, when compared to the reaction cascade conducted at 60 °C (Table 2, entry 3). A control experiment using only diphenylphosphate (10 mol %) revealed that no cyclization took place even after heating at 60 °C for 24 h (Table 2, entry 11), thus highlighting the critical role of the Au catalyst in the hydroamination process. Finally, a control experiment using no acid additive yielded none of the desired **5a** (Table 2, entry 12), thus confirming the need for amine protonation prior to the hydroamination stage.

With optimal conditions identified, a range of substituted aromatic *N*-Boc-protected aldimines were subjected to the enantioselective nitro-Mannich/hydroamination cascade (Table 3). The reaction was found to tolerate both *o*- and *m*-toluene derived *N*-Boc-protected aldimines, affording the desired products in good yields and high enantioselectivities (Table 3, entries 2 and 3). A range of electron-poor *o*-, *m*- and *p*-halogen substituted aromatic aldimines (Table 3, entries 4–7) all furnished the desired tetrahydropyridines **5d**–**g** in good yields (49–63%) and high enantioselectivities (87–96%).

In contrast, more electron-rich *m*-substituted methoxy and 2-thienyl derived aldimines (Table 3, entries 8 and 9) afforded the products **5h** and **5i** in lower yields (31–54%) while retaining good enantioselectivities (88–93%). The 1- and 2-naphthyl derived aldimines (Table 3, entries 10 and 11)

(12) For recent examples using Echavarren's catalyst, see: (a) López-Carrillo, V.; Echavarren, A. M. *J. Am. Chem. Soc.* **2010**, *132*, 9292–9294. (b) Solorio-Alvarado, C. R.; Wang, Y.; Echavarren, A. M. *J. Am. Chem. Soc.* **2011**, *133*, 11952–11955.

(13) Very few examples of intramolecular 6-*exo*-*dig* hydroamination reactions between *N*-Boc protected amines and alkynes have been reported. For examples, see: (a) Ritter, S.; Horino, Y.; Lex, J.; Schmalz, H.-G. *Synlett* **2006**, 3309–3313. (b) Enomoto, T.; Obika, S.; Yasui, Y.; Takemoto, Y. *Synlett* **2008**, 1647–1650.

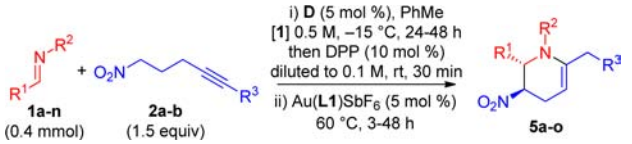
(14) The diastereoselectivity of the crude reaction mixture was typically higher than expected from the ratio of diastereomers in the nitro-Mannich product due to both a slow rate of cyclization of **4** (relative to **3**) and a competing decomposition pathway. Evidence of this was provided in the synthesis of tetrahydropyridine **5a**. During purification of **5a** (Table 3, entry 1), unreacted β-nitroamine **4** was recovered in 6% yield and 82% *ee*, while none of the β-nitroamine **3** was observed. See SI for details.

(15) The enhancement in diastereomeric ratio on purification was a result of epimerization of the less stable *cis*-isomer to the more stable *trans*-isomer during silica gel chromatography. See SI for details.

(16) For details of the nitro-Mannich reaction diastereoselectivity for compounds **5a**–**n**, **3o**, and **4o**, see the SI.

(17) The absolute configuration of tetrahydropyridine **5f** was determined to be (2*S*,3*R*) by single crystal X-ray diffraction. All other compound structures were assigned by analogy to **5f** assuming a uniform reaction pathway. Data for **5f** were collected at 150 K [Cosier, J.; Glazer, A. M. *J. Appl. Crystallogr.* **1986**, *19*, 105–107] using an Enraf-Nonius KCCD Diffractometer [Otwinowski, Z.; Minor, W. *Processing of X-ray Diffraction Data Collected in Oscillation Mode, Methods in Enzymology*; Carter, C. W., Jr., Sweet, R. M., Eds.; Academic Press: New York, 1997; Vol. 276, pp 307–326] solved with SIR92 [Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. *J. Appl. Crystallogr.* **1994**, *27*, 435] and refined using the CRYSTALS software suite [Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487. Cooper, R. I.; Thompson, A. L.; Watkin, D. J. *J. Appl. Crystallogr.* **2010**, *43*, 1100–1107] as per the SI. CCDC-890291 contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

**Table 3.** Scope of the One-Pot Enantioselective Nitro-Mannich/Hydroamination Cascade[16]



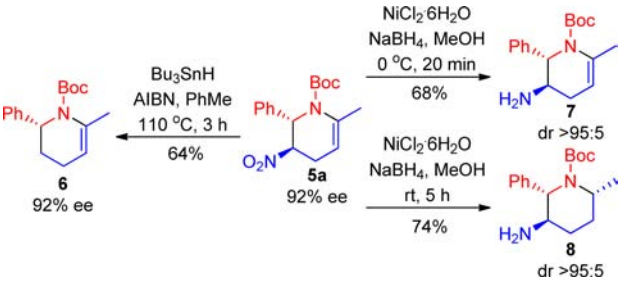

| entry | $R^1$ | $R^2$ | $R^3$ | (i) time/h | (ii) time/h | 5 | dr[a] | yield (%)[b] | dr[c] | *ee* (%)[d] |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Ph | Boc | H | 24 | 8 | **a** | 92:8 | 66 | >98:2 | 92 |
| 2 | *o*-$MeC_6H_4$ | Boc | H | 48 | 10 | **b** | 95:5 | 49 | 97:3 | 86 |
| 3 | *m*-$MeC_6H_4$ | Boc | H | 32 | 15 | **c** | 86:14 | 72 | 98:2 | 91 |
| 4 | *m*-$FC_6H_4$ | Boc | H | 24 | 15 | **d** | 95:5 | 56 | 98:2 | 93 |
| 5 | *p*-$FC_6H_4$ | Boc | H | 26 | 3 | **e** | 96:4 | 49 | 97:3 | 92 |
| 6 | *o*-$ClC_6H_4$ | Boc | H | 48 | 28 | **f**[e] | 89:11 | 51 | 94:6 | 87 |
| 7 | *m*-$BrC_6H_4$ | Boc | H | 24 | 7 | **g** | 95:5 | 63 | 98:2 | 96 |
| 8 | *m*-$MeOC_6H_4$ | Boc | H | 24 | 6 | **h** | 94:6 | 54 | 98:2 | 93 |
| 9 | 2-thienyl | Boc | H | 24 | 24 | **i** | 88:12 | 31 | 95:5 | 88 |
| 10 | 1-naphthyl | Boc | H | 48 | 24 | **j** | 95:5 | 55 | >98:2 | 88 |
| 11 | 2-naphthyl | Boc | H | 24 | 48 | **k** | 95:5 | 62 | >98:2 | 86 |
| 12 | Ph | Cbz | H | 24 | 16 | **l** | 93:7 | 50 | >98:2 | 93 |
| 13 | *p*-$F_3CC_6H_4$ | Cbz | H | 24 | 28 | **m** | 95:5 | 55 | 98:2 | 95 |
| 14 | *p*-$ClC_6H_4$ | Cbz | H | 24 | 24 | **n** | 94:6 | 62 | 96:4 | 94 |
| 15[f] | Ph | Boc | Ph | 32 | 72 | **o** | — | — | — | — |

[a] Determined by $^1$H NMR analysis of the crude reaction mixture. [b] Isolated yield after flash column chromatography. [c] dr of the purified product determined by $^1$H NMR analysis. [d] *ee* of the major diastereomer determined by HPLC anaylsis. [e] Absolute and relative stereochemistry of the major diastereomer was determined by single crystal X-ray analysis.[17] [f] No cyclization observed at 100 °C; nitro-Mannich adducts **3o** and **4o** were recovered.

gave rise to the desired tetrahydropyridine products in good yields (55–62%) and enantioselectivities (86–88%). *N*-Cbz aldimines were fully compatible with the developed nitro-Mannich/hydroamination cascade (Table 3, entries 12–14), and tetrahydropyridines **5l**–**n** were afforded in good yields (50–62%) and high enantioselectivities (93–95%). Phenyl substituted nitro-alkyne substrate **2b** (Table 3, entry 15) did undergo the nitro-Mannich reaction but failed to perform the Au-catalyzed cyclization even after heating at 100 °C for 72 h.[18] The nitro-Mannich adducts **3o** and **4o** were recovered as an inseparable mixture of diastereomers in 63% combined yield with 90% *ee* being obtained for the major diastereomer.

To highlight the synthetic potential of the tetrahydropyridine cascade products, **5a** was further elaborated by a variety of methods (Scheme 2). Firstly, reductive removal of the nitro group using Ono's conditions[19] occurred smoothly to give tetrahydropyridine **6** in 64% yield. A partially chemoselective reduction of the nitro group was achieved using *in situ* prepared nickel boride in chilled methanol, furnishing the desired amine **7** in 68% yield with excellent diastereoselectivity. The fully reduced piperidine **8** was also isolated from the reaction mixture as a single diastereomer in 28% yield. Increasing the equivalents of nickel boride, reaction time, and temperature facilitated exhaustive reduction to piperidine **8**, which was isolated in 74% yield as a single diastereomer.

**Scheme 2.** Synthetic Elaboration of Tetrahydropyridine **5a**




In summary, we have developed a novel one-pot enantioselective synthesis of *N*-Boc and *N*-Cbz-protected tetrahydropyridine derivatives using a nitro-Mannich/hydroamination cascade. The reaction utilizes readily available and easily synthesized starting materials to generate a high level of molecular complexity in a one-pot procedure. A total of 14 examples have been synthesized with yields ranging from 31 to 72% and enantioselectivities ranging from 86 to 96%. Further investigation into the synthesis of other chemical entities using nitro-Mannich/hydroamination cascades is currently underway, and the results will be reported in due course.

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**Supporting Information Available.** Experimental procedures and spectral data for compounds **1m**, **2a**–**b**, **3**, **4**, **5a**–**n**, **3o**, **4o**, and **6**–**8** and the CIF file for compound **5f**. This material is available free of charge via the Internet at http://pubs.acs.org.

(18) It is possible that the phenyl substituted alkyne substrates **3o** and **4o** do not undergo 6-*exo*-*dig* cyclization due to 1,3-allylic strain arising in the transition state. For a related gold catalyzed carbocyclization to an alkyne, see: (a) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526–4527. (b) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 5350–5352.

(19) For seminal work, see: (a) Ono, N.; Miyake, H.; Tamura, R.; Kaji, A. *Tetrahedron Lett.* **1981**, *22*, 1705–1708. (b) Tanner, D. D.; Blackburn, E. V.; Diaz, G. E. *J. Am. Chem. Soc.* **1981**, *103*, 1557–1559.

The authors declare no competing financial interest.