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# Diastereoselective Synthesis of 4-Hydroxypiperidin-2-ones via Cu(I)-Catalyzed Reductive Aldol Cyclization†

**Hon Wai Lam,* Gordon J. Murray, and James D. Firth**

*School of Chemistry, University of Edinburgh, The King's Buildings, West Mains Road, Edinburgh EH9 3JJ, United Kingdom*

*h.lam@ed.ac.uk*

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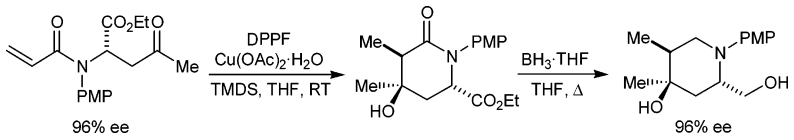
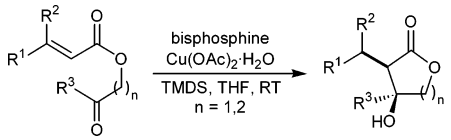
## ABSTRACT




**4-Hydroxypiperidin-2-ones may be prepared in highly diastereoselective fashion using a Cu(I)-catalyzed reductive aldol cyclization of α,β-unsaturated amides with ketones. Used in combination with proline-catalyzed asymmetric Mannich reactions, this methodology enables the enantioselective synthesis of more highly functionalized piperidin-2-ones and hydroxylated piperidines.**

Metal-mediated cyclization reactions provide the basis for many powerful methods of carbocyclic and heterocyclic ring construction.[1] Within this field, intramolecular reductive aldol[2] and Michael[2c,h,3] reactions have proven to be of high utility. These processes are initiated by the hydrometalation of an α,β-unsaturated carbonyl compound, allowing the regioselective generation of a metal enolate under mild reaction conditions. Subsequent intramolecular trapping of the enolate with an appropriate electrophile leads to the cyclic product, often with high levels of diastereoselectivity. The majority of such processes reported thus far have been concerned with the preparation of carbocycles; however, we recently reported a copper(I)-bisphosphine catalyzed reductive aldol cyclization (eq 1) that affords a variety of five-




(1)

and six-membered β-hydroxylactones in moderate to good yields and with moderate enantioselectivites when suitable chiral bisphosphines are employed.[4] Herein we describe the extension of this process to the synthesis of 4-hydroxypiperidin-2-ones through the use of the corresponding substrates containing an amide linkage in place of an ester.

† Dedicated to Prof. David A. Evans on the occasion of his 65th birthday.

(1) For representative examples, see: (a) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890−3908. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945−2964. (c) Negishi, E.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365−393. (d) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635−662.

(2) (a) Koech, P. K.; Krische, M. J. *Org. Lett.* **2004**, *6*, 691−694. (b) Huddleston, R. R.; Krische, M. J. *Org. Lett.* **2003**, *5*, 1143−1146. (c) Wang, L.-C.; Jang, H.-Y.; Roh, Y.; Lynch, V.; Schultz, A. J.; Wang, X.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 9448−9453. (d) Jang, H.-Y.; Huddleston, R. R.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 15156−15157. (e) Chiu, P.; Leung, S. K. *Chem. Commun.* **2004**, 2308−2309. (f) Chiu, P.; Szeto, C.-P.; Geng, Z.; Cheng, K.-F. *Org. Lett.* **2001**, *3*, 1901−1903. (g) Freiría, M.; Whitehead, A. J.; Tocher, D. A.; Motherwell, W. B. *Tetrahedron* **2004**, *60*, 2673−2692. (h) Miura, K.; Yamada, Y.; Tomita, M.; Hosomi, A. *Synlett* **2004**, 1985−1989.

(3) (a) Hori, K.; Hikage, N.; Inagaki, A.; Mori, S.; Nomura, K.; Yoshii, E. *J. Org. Chem.* **1992**, *57*, 2888−2902. (b) Hori, K.; Kazumo, H.; Nomura, K.; Yoshii, E. *Tetrahedron Lett.* **1993**, *34*, 2183−2186. (c) Yoshii, E.; Hori, K.; Nomura, K.; Yamaguchi, K. *Synlett* **1995**, 568−570. (d) Yoshizaki, H.; Tanaka, T.; Yoshii, E.; Koizumi, T.; Takeda, K. *Tetrahedron Lett.* **1998**, *39*, 47−50. (e) Takeda, K.; Ohkawa, N.; Hori, K.; Koizumi, T.; Yoshii, E. *Heterocycles* **1998**, *47*, 277−282. (f) Suwa, T.; Nishino, K.; Miyatake, M.; Shibata, I.; Baba, A. *Tetrahedron Lett.* **2000**, *41*, 3403−3406. (g) Kamenecka, T. M.; Overman, L. E.; Ly Sykata, S. K. *Org. Lett.* **2002**, *4*, 79−82.

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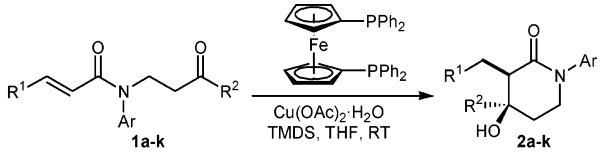
**Table 1.** Catalytic Reductive Aldol Cyclizations To Form 4-Hydroxypiperidin-2-ones[a]

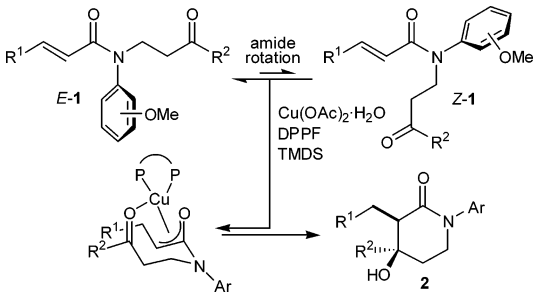



| entry | substrate | | product | | time (h) | yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | | R = Me **1a** | | **2a** | 2.5 | 66 |
| 2 | | R = Et **1b** | | **2b** | 5.5 | 61 |
| 3 | | R = *i*-Bu **1c** | | **2c** | 24 | 64 |
| 4[c] | | R = Ph **1d** | | **2d** | 21 | 69 |
| 5 | | R = 4-MeC$_6$H$_4$ **1e** | | **2e** | 24 | 64 |
| 6 | | R = 2-furyl **1f** | | **2f** | 24 | 53 |
| 7[c] | | R = Me **1g** | | **2g** | 22 | 55 |
| 8 | | R = Et **1h** | | **2h** | 24 | 52 |
| 9 | | **1i** | | **2i** | 4 | 70 |
| 10 | | R = Me **1j** | | **2j** | 24 | 70 |
| 11[d] | | R = Ph **1k** | | **2k** | 23 | 65 |

[a] Reactions were conducted using 1.0 mmol of substrate, 5 mol % Cu, 5 mol % DPPF, and 1.0 mmol of TMDS in 5 mL of THF. [b] Isolated yield. [c] Conducted using 0.2 mL of substrate, 5 mol % Cu, 5 mol % DPPF, and 0.2 mmol of TMDS in 2 mL of THF. [d] (EtO)$_2$MeSiH (2.0 mmol) was employed in place of TMDS. PMP = *p*-methoxyphenyl, OMP = *o*-methoxyphenyl.

To increase the synthetic versatility of the products, we elected to examine the reactions of substrates **1** containing a removal nitrogen substituent, and PMP (*p*-methoxyphenyl) and OMP (*o*-methoxyphenyl) groups were chosen for this study.[5] *N*-Alkyl-*N*-arylamides such as **1** are known to exist predominantly as the *E*-amide rotamer, with the aryl group twisted such that the plane of the aromatic ring is approximately perpendicular to that of the amide group (Scheme 1).[6] At the outset of these investigations, it was not clear whether this rotamer distribution would have any impact on the ability of these substrates to undergo cyclization.

**Scheme 1.** Rotational Isomers of Cyclization Precursors **1**



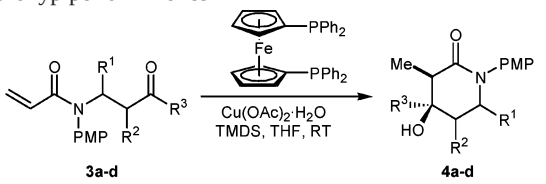

In the event, using the conditions described previously for the corresponding ester substrates[4] (5 mol % Cu(OAc)$_2$·H$_2$O, 5 mol % 1,1′-bis(diphenylphosphino)-ferrocene (DPPF), and 1 equiv of 1,1,3,3-tetramethylhydrosiloxane (TMDS) in THF at room temperature), a range of substrates **1a**−**k** underwent cyclization to form 4-hydroxypiperidin-2-ones **2a**−**k** (Table 1). The reaction proved to be tolerant to wide variation in the ketone component, with alkyl (entries 1−3 and 7−10), aromatic (entries 4, 5, and 11), and heteroaromatic (entry 6) ketones reacting readily. However, the reaction was less tolerant of substitution in the α,β-unsaturated carbonyl component. Acryloyl amides were found to be the best substrates, giving the desired piperidin-2-one products for all cases examined (entries 1−6 and 9). Although crotonoyl amides also underwent cyclization (entries 7, 8, 10, and 11), reaction rates and conversions were generally lower.[7] In the case of substrate **1k**, use of (EtO)$_2$MeSiH in place of TMDS proved to be beneficial (entry 11). The reactions

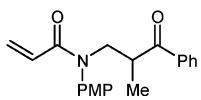
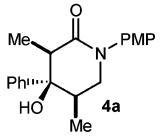
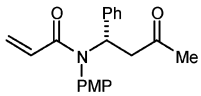
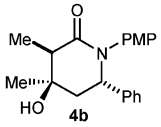
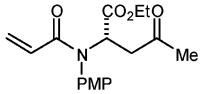
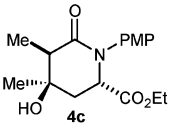
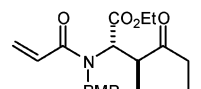
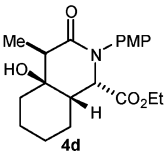
(5) PMP and OMP groups may be removed oxidatively, for example, using ceric ammonium nitrate (CAN). See: (a) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765−2768. (b) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153−7154. For the removal of OMP groups using PhI(OAc)$_2$, see: (c) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409−10410.

(6) (a) Pederson, B. F.; Pederson, B. *Tetrahedron Lett.* **1965**, *6*, 2995−3001. (b) Itai, A.; Toriumi, Y.; Tomioka, N.; Kagechika, H.; Azumaya, I.; Shudo, K. *Tetrahedron Lett.* **1989**, *30*, 6177−6180. (c) Curran, D. P.; Hale, G. R.; Geib, S. J.; Balog, A.; Cass, Q. B.; Degani, A. L. G.; Hernandes, M. Z.; Freitas, L. C. G. *Tetrahedron: Asymmetry* **1997**, *8*, 3955−3975.

(7) As the size of the substituent on the α,β-unsaturated amide is increased further, the formation of uncyclized side products resulting from both ketone reduction and conjugate reduction also becomes problematic.

**Table 2.** Formation of C5- and C6−Substituted 4-Hydroxypiperidin-2-ones[a]




| entry | substrate | product | dr[b] | yield (%)[c] |
|---|---|---|---|---|
| 1 |  |  | 8:1 | 78 |
| | **3a** | **4a** | | |
| 2 |  |  | >19:1 | 65 |
| | **3b** 85% ee | **4b** | | |
| 3 |  |  | >16:1 | 68 |
| | **3c** 96% ee | **4c** | | |
| 4 |  |  | 5:1 | 66 |
| | **3d** >99% ee | **4d** | | |

[a] Reactions were conducted using 0.2 mmol of substrate, 5 mol % Cu, 5 mol % DPPF, and 0.2 mmol of TMDS in 2 mL of THF for 2−24 h. [b] Determined by $^1$H NMR analysis of the unpurified reaction mixtures. Minor diastereomers (not shown) are assumed to possess inverted configurations at C3 and C4. [c] Isolated yield of major diastereomer.

proceeded with high diastereoselectivities (>95:5 by $^1$H NMR analysis), and the relative configurations of the products[8] were found to match those of the lactone products described previously.[4]

We next examined the effect of preexisting stereocenters in the tether linking the amide and the ketone on the diastereoselectivity of the process (Table 2). Acrylamide **3a**, containing a methyl substituent α to the ketone, cyclized to give a mixture of two diastereomers in a ratio of 8:1, from which piperidinone **4a** was isolated in 78% yield (entry1). By employing L-proline-catalyzed direct asymmetric Mannich reactions to prepare the requisite $\beta$-aminoketones,[9] we were able to access acrylamides **3b**−**3d** in enantiomerically enriched form, and these cyclized to give piperidinones **4b**−**4d**, respectively, as the major products (entries 2−4).[10] The

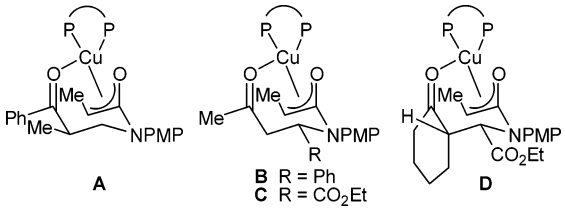
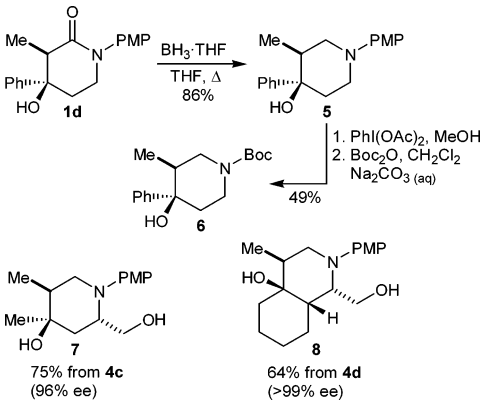



**Figure 1.** Possible reactive conformations for the cyclization of substrates **3a**−**d**.

moderate to excellent levels of 1,2- and 1,3-asymmetric induction in these reactions may be rationalized by invoking the chelated chairlike conformations **A**−**D** shown in Figure 1, with substituents in the tether linking the amide enolate and the ketone preferring to adopt pseudoequatorial positions.[11]

The synthetic utility of the piperidinone products was illustrated by a number of transformations. Reductive removal of the carbonyl group allows entry to the piperidine ring system, a ubiquitous structural feature of many natural products and biologically important compounds.[12] For example, treatment of **1d** with borane at reflux provided piperidine **5** in good yield, which could be converted into **6** by oxidative removal of the PMP group[5c] followed by in situ treatment of the resulting amine with $Boc_2O$ (Scheme 2). The amide reduction of piperidin-2-ones **4c** and **4d** with

**Scheme 2.** Conversion of Piperidinone Products into Piperidines




borane was accompanied by reduction of the ethyl esters to give piperidines **7** and **8**, respectively. Polyhydroxylated piperidines are of considerable biological interest due to their potential to act as glycosidase inhibitors.[13]

(8) The relative configurations of the piperidinones **2a**, **2d**, and **2g** were confirmed by X-ray crystallography. See Supporting Information for details. The stereochemistries of the remaining products were assigned by analogy.

(9) (a) Notz, W.; Watanabe, S.-I.; Chowdari, N. S.; Zhong, G.; Betancort, J. M.; Tanaka, J.; Barbas, C. F., III. *Adv. Synth. Catal.* **2004**, *346*, 1131−1140. See also: (b) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827−833. (c) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336−9337.

(10) The stereochemistries of the piperidinones **4a**, **4c**, and **4d** were determined by X-ray crystallography. Analysis of $^1$H NMR coupling constants was used to establish the stereochemistry of **4b**. See Supporting Information for details.

(11) For related cyclizations involving the $SmI_2$-promoted intramolecular Reformatsky reactions of $\beta$-haloacetoxyketones and an excellent discussion of the factors determining the stereochemical outcomes, see: Molander, G. A.; Etter, J. B.; Harring, L. S.; Thorel, P.-J. *J. Am. Chem. Soc.* **1991**, *113*, 8036−8045.

(12) For reviews of piperidine synthesis, see: (a) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953−2989. (b) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781−1813.

In summary, we have applied copper(I)-catalyzed reductive aldol cyclizations to the highly diastereoselective synthesis of 4-hydroxypiperidin-2-ones. L-Proline-catalyzed Mannich reactions may be used to prepare more highly substituted cyclization precursors in enantiomerically enriched form, enabling the enantioselective synthesis of piperidin-2-ones and piperidines. Current work is focused on identifying catalyst systems that allow a greater range of substituted $\alpha,\beta$-unsaturated amides to become viable substrates, developing enantioselective variants of this process, and applying this methodology to other substrate classes. The results from these studies will be reported in due course.

(13) For a recent review, see: Pearson, M. S. W.; Mathé-Allainmat, M.; Fargeas, V.; Lebreton, J. *Eur. J. Org. Chem.* **2005**, 2159−2191.

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**Supporting Information Available:** Experimental procedures, full spectroscopic data for all new compounds, and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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