Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 3965–3968
Tetrahedron Letters

Enantioselective addition of aldehydes to amines via combined catalytic biomimetic oxidation and organocatalytic C–C bond formation

Ismail Ibrahem, Joseph S. M. Samec, Jan E. Bäckvall* and Armando Córdova*

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden

Received 27 February 2005; revised 3 April 2005; accepted 12 April 2005

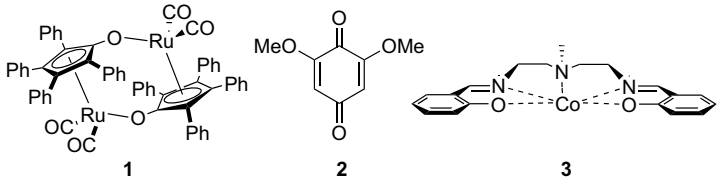
Abstract—The biomimetic catalytic enantioselective addition of aldehydes to amines is reported. This was accomplished by combining biomimetic coupled catalytic aerobic oxidation of amines involving ruthenium-induced dehydrogenation and organocatalytic asymmetric Mannich reactions. The novel one-pot reactions furnished β-amino aldehyde and α-amino acid derivatives in high yields with excellent chemoselectivity and up to >99% ee.

Oxidation is a fundamental reaction in Nature as well as in organic chemistry.[1] The terminal oxidants used in nature are molecular oxygen and hydrogen peroxide. These oxidants are, from both economical and environmental standpoints, also the superior terminal oxidants, used in chemical applications. This has led to an intense search to find substrate-selective catalysts to achieve efficient oxidations using molecular oxygen.[2] The challenge when using transition metals is to overcome the high-energy pathway for reoxidation of the metal. This has led to the development of biomimetic oxidations, where the large jump in oxidation potential is divided into smaller changes by the use of several electron transfer mediators (ETMs).[1,2]

The employment of small organic molecules as catalysts in asymmetric synthesis has experienced a renaissance in organic chemistry. In particular, amino acid-derived catalysts have been proved successful in the asymmetric construction of chiral molecules.[3]

Intrigued by Nature's way of constructing complex molecules from simple achiral organic molecules via enzyme-catalyzed pathways, we became interested in whether it would be possible to combine biomimetic catalytic aerobic oxidations with tandem organocatalytic C–C bond-forming reactions.[3,4] This novel reaction sequence would mimic the connection of two separate fundamental biochemical pathways of cells. The coupled catalytic aerobic oxidation of amines involving ruthenium-induced dehydrogenation, which generates imines,[5] linked with tandem direct amino acid-catalyzed cross-Mannich reactions would serve as a potential model system (Scheme 1).[6]

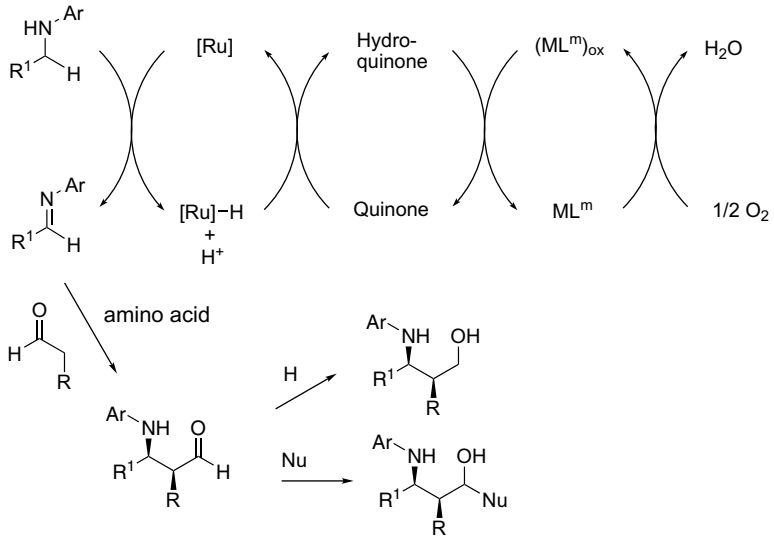
In addition, the combination of these two catalytic processes would be a new entry to chiral β-amino aldehydes, which are susceptible to further chemical manipulation and yield pharmaceutically important γ-amino alcohols and β-amino acids.[7] Herein, we report the first combination of transition metal-catalyzed



1 2 3

Keywords: Biomimetic oxidation; Catalysis; Asymmetric synthesis; Ruthenium; Proline.
* Corresponding authors. Tel.: +46 8 162479; fax: +46 8 154908; e-mail addresses: jeb@organ.su.se; acordova1a@netscape.net; acordova@organ.su.se

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.04.047



Scheme 1. Combination of catalytic aerobic oxidation of amines with tandem direct amino acid-catalyzed asymmetric Mannich-type reactions.

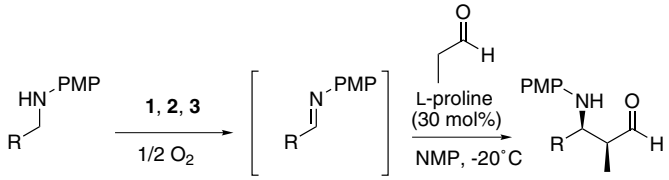
aerobic oxidations with direct organocatalytic enantioselective Mannich reactions furnishing β-amino aldehydes, γ-amino alcohols and α-amino acid derivatives in up to >95% yield with excellent chemoselectivity and >99% ee.

In an initial experiment (Table 1, entry 1), reaction of benzyl-*p*-methoxyphenyl (PMP)-amine in toluene at 110 °C with O_2 in the presence of ruthenium complex **1**, quinone **2** and cobalt complex **3** afforded the corresponding imine. After 24 h, the mixture was cooled to room temperature and the solvent was removed under reduced pressure. Next, *N*-methyl-pyrrolidinone (NMP) and L-proline (30 mol %) were added to the reaction mixture and then propionaldehyde was added at −20 °C. After 16 h the reaction temperature was increased to 0 °C and the catalytically generated β-amino aldehyde **4** was reduced in situ to the corresponding γ-amino alcohol by addition of excess $NaBH_4$. The crude product was isolated by silica gel column chromatography (EtOAc/pentane mixtures) to yield the corresponding γ-amino alcohol quantitatively with >99% ee.

Encouraged by this result, we investigated the one-pot combination of catalytically linked aerobic oxidations and direct catalytic enantioselective Mannich additions to a set of secondary PMP *N*-protected amines (Table 1).[8] The PMP group was chosen since it can be readily removed to give the free amine.[6a–c]

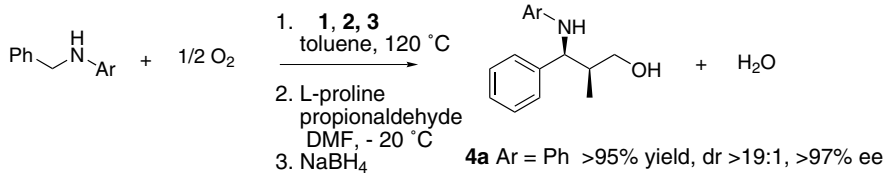
The one-pot tandem catalytic reactions proceeded smoothly furnishing β-amino aldehydes **4**–**12** with excellent diastereo- and enantioselectivities. For example, the β-formyl amino acid ester **11** was reduced in situ to the

Table 1. Direct catalytic enantioselective addition of aldehydes to amines



Entry	R	Product	Yield (%)[a]	Dr[b]	ee (%)[c]
1	Ph	**4**	>95	>19:1	>99
2	2-Naphthyl	**5**	>95	15:1	76
3	4-BrC_6H_4	**6**	76	>19:1	>99
4	4-MeC_6H_4	**7**	75	8:1	98
5	4-$MeOC_6H_4$	**8**	63	10:1	98
6	2-Furyl[d]	**9**	99	6:1	>99
7	3-Pyridyl[d]	**10**	>95	>19:1	>99
8	CO_2Et[d]	**11**	>95[e]	>19:1	>99
9	4-FC_6H_4	**12**	>95	15:1	99

[a] Isolated overall yield after silica-gel column chromatography of the γ-amino alcohol obtained by in situ reduction of the β-amino aldehydes.
[b] Determined by NMR.
[c] Determined by Chiral-phase HPLC analyses. All isolated products were in accordance with previously reported compounds.[6]
[d] 8 mol % of **1**.
[e] The oxidation was run for 72 h.



Scheme 2. One-pot catalytic asymmetric synthesis of 1,3-amino alcohols.

corresponding L-homoserine derivative, which was quantitatively isolated as a single diastereomer with >99% ee. The reactions proceeded with excellent chemoselectivity and the ruthenium complex **1** did not oxidize or affect the ee's of the β-amino aldehyde products. The combination of one-pot coupled catalytic aerobic oxidations of amines with tandem catalytic asymmetric crossed-Mannich reactions circumvented the isolation of the imines prior to the nucleophilic additions. In addition, the procedure decreases the generation of waste products and could be used directly in other small molecule-catalyzed enantioselective Mannich-type reactions.[9] The employment of 30 mol % L-proline together with the use of NMP as the reaction media significantly improved the efficiency of the reaction and the products were isolated in excellent yields.

The coupled catalytic aerobic oxidation of amines was also efficient in the generation of ketimines. However, proline only furnished trace amounts of Mannich products in reactions with aromatic ketimines. The coupled one-pot aerobic oxidation of amines was also successfully linked with direct proline-catalyzed Mannich reactions using aliphatic aldehydes and ketones as donors. For example, employing the one-pot tandem catalytic combination of aerobic oxidation and Mannich-type addition to benzyl-*p*-methoxyphenyl-amine using acetone as the donor furnished the corresponding Mannich adduct in 65% overall yield with 98% ee. Furthermore, the *p*-methoxyphenyl moiety of the amine can be readily changed to other aryl groups (Scheme 2). For example, 1,3-amino alcohol **4a** was synthesized in a one-pot sequence from the corresponding amine in >95% yield with >97% ee.

The aldehyde moiety of the Mannich adducts is susceptible to further nucleophilic attack and therefore further tandem reactions such as cyanation or allylation can be linked to the one-pot tandem reactions.[6c] The absolute stereochemistry of the Mannich adducts was in accordance with previous proline-catalyzed asymmetric crossed-Mannich reactions.[6] Hence, L-proline furnished *syn*-(2*S*,3*S*)-Mannich adducts.

In conclusion, we have reported a novel biomimetic direct catalytic asymmetric addition of aldehydes to amines and this constitutes a formal C–H activation.[10] The first one-pot combination of catalytically sequenced aerobic oxidation of amines involving ruthenium-induced dehydrogenation and tandem direct amino acid-catalyzed enantioselective Mannich reactions enabled this transformation. The catalytic cascade of reactions proceed with excellent chemoselectivity and enzyme-like selectivity. The reactions can be readily scaled-up and provide a low cost entry for either enantiomer of α-amino acid and γ-amino alcohol derivatives. Further studies on the combination of catalytic coupled aerobic oxidation and organocatalysis are ongoing.

Acknowledgements

A.C. thanks the Swedish Natural Science Research Council and Wenner-Gren foundation for financial support. J.E.B. thanks the Swedish Natural Science Research Council and the Swedish Foundation for Strategic Research.

References and notes

1. (a) *Modern Oxidation Methods*; Bäckvall, J.-E., Ed.; Wiley-VCH: Weinheim, 2004; (b) Industrial Organic Chemicals: Starting Materials and Intermediates, an Ullman's Encyclopedia; Wiley-VCH: Weinheim, 1999.
2. Sheldon, R. A. *Green Chem.* **2000**, *2*, G1.
3. Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726; Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138; List, B. *Tetrahedron* **2002**, *58*, 5573; Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481; Merino, P.; Tejero, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 2995.
4. Bäckvall, J.-E.; Hopkins, R. B.; Grennberg, H.; Mader, M.; Awasthi, A. K. *J. Am. Chem. Soc.* **1990**, *112*, 5160; Bergstad, K.; Jonsson, S. Y.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1999**, *121*, 10424; Jonsson, S. Y.; Färnegård, K.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2001**, *123*, 1365; Jonsson, S. Y.; Adolfsson, H.; Bäckvall, J.-E. *Chem. Eur. J.* **2003**, *9*, 278; Csjernyik, G.; Éll, A. H.; Fadini, L.; Pugin, B.; Bäckvall, J.-E. *J. Org. Chem.* **2002**, *67*, 1657; Markó, I. E.; Giles, P. R.; Tsukazaki, M.; Brown, S. M.; Urch, C. J. *Science* **1996**, *274*, 2044; Dijksman, A.; Marino-Conzales, A.; Mariata i Payeras, A.; Arends, I. W. C. E.; Sheldon, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 6826; Liu, R.; Liang, X.; Dong, C.; Hu, X. *J. Am. Chem. Soc.* **2004**, *126*, 4112; Yang, G.; Ma, Y.; Xu, J. *J. Am. Chem. Soc.* **2004**, *126*, 10542; Córdova, A.; Sundén, H.; Enqvist, M.; Ibrahem, I.; Casas, J. *J. Am. Chem. Soc.* **2004**, *126*, 8914; Sundén, H.; Engqvist, M.; Casas, J.; Ibrahem, I.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 6532.
5. Samec, J. S. M.; Éll, A. H.; Bäckvall, J.-E. *Chem. Eur. J.*, in press.
6. (a) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336; (b) Córdova, A. *Chem. Eur. J.* **2004**, *10*, 1987; (c) Córdova, A. *Acc. Chem Res.* **2004**, *37*, 102; (d) Córdova, A. *Synlett* **2003**, 1651; (e) Hayashi, Y.; Tsuboi, W.; Ashimine, J.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3677; (f) Córdova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas, C. F., III *J. Am. Chem. Soc.* **2002**, *124*,

1866; (g) Ibrahem, I.; Córdova, A. *Tetrahedron Lett.* **2005**, *46*, 2839.

7. *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: Weinheim, 1997; Kleinan, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pegamon: New York, 1991; Vol. 2, Chapter 4.1; Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015.
8. In a typical experiment, ruthenium complex **1** (10.8 mg, 10 μmol, 4 mol %), quinone **2** (8.4 mg, 50 μmol, 20 mol %) and cobalt complex **3** (4 mg, 5 μmol, 4 mol %) were charged into a 5 mL round-bottomed flask under an argon atmosphere. The amine (1 mL, 0.125 M in toluene, 0.125 mmol) was added to this mixture followed by flushing with air for ca. 1 min. A stream of air was allowed to pass through the system and the mixture was heated to 110 °C in an oil bath. After 24 h, the mixture was cooled to room temperature and the solvent was removed under reduced pressure. Next, *N*-methylpyrrolidinone (NMP, 1 mL) and L-proline (30 mol %) were added to the reaction flask and the temperature was decreased to −20 °C followed by addition of propionaldehyde (0.75 mmol) in one portion. After 16 h the reaction temperature was increased to 0 °C and MeOH (2 mL) was added followed by portionwise addition of $NaBH_4$. The reaction was quenched by addition of 1 N HCl solution and extraction with EtOAc (3×15 mL). The combined dried organic extracts were concentrated and the crude product purified by silica-gel column chromatography (pentane/EtOAc mixtures) affording the corresponding 1,3-amino alcohols. The ees of the amino alcohols were determined by Chiral-phase HPLC analyses using a Chiralpak AD column.
9. (a) Trost, B. M.; Terrell, L. M. *J. Am. Chem. Soc.* **2003**, *125*, 338; (b) Zhuang, W.; Saaby, S.; Jørgansen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4476; (c) Cobb, A. J. A.; Shaw, D. M.; Ley, S. V. *Synlett* **2004**, 558.
10. (a) For a recent transition metal-catalyzed alkynylation and arylation of sp^3 C–H bonds adjacent to a nitrogen see: Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810; (b) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2004**, *126*, 13244.