Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 1498–1501
Tetrahedron Letters

Direct asymmetric aldol reactions catalyzed by nanocrystalline copper(II) oxide

M. Lakshmi Kantam *, Thekkathu Ramani, Lakkoju Chakrapani, K. Vijay Kumar

Inorganic and Physical Chemistry Division, Indian Institute of Chemical Technology, Hyderabad 500 007, India

Received 17 September 2007; revised 19 December 2007; accepted 24 December 2007
Available online 8 January 2008

Abstract

The direct asymmetric aldol reactions of aromatic and heteroaromatic aldehydes with acetone to afford chiral β-hydroxy carbonyl compounds in good yields and good to moderate enantioselectivities are realized using nanocrystalline copper(II) oxide in the presence of (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine at −30 °C. The catalyst can be reused for four cycles with consistent activity and enantioselectivity.

Keywords: Direct asymmetric aldol reaction; Nano-CuO; Enantiomeric excess (ee); β-Hydroxy carbonyl compounds

Direct asymmetric aldol reactions provide one of the most powerful tools for constructing optically active β-hydroxy carbonyl compounds. The aldol reaction is widely used in synthetic organic chemistry to generate intermediates for anti-hypertensive drugs and calcium antagonists.[1] Chiral β-hydroxy carbonyl compounds can be readily converted to 1,3-*syn*- and *anti*-diols and amino alcohols, which are the building blocks for antibiotics, pheromones, and many biologically active compounds.[2]

The direct aldol reaction, starting from an aldehyde and an unmodified ketone, is highly atom efficient[3] compared with the process in which the preconversion of a ketone into a more reactive species such as an enol silyl ether, enol methyl ether, or ketone silyl acetal as the aldol donor (Mukaiyama aldol reaction) is required.[4,5] Since the control of stereochemistry during aldol additions is a crucial problem, the metal catalyzed direct asymmetric aldol reaction of aldehydes with unmodified ketones still remains a challenge for synthetic chemists.[6]

Shibasaki et al. achieved the first catalytic asymmetric aldol reaction between aldehydes and unmodified ketones by using heterobimetallic multifunctional catalysts.[7,8] Later, direct asymmetric aldol reactions with good to excellent enantioselectivities (ee's) were accomplished using transition metal catalysts.[9,10] Moreover, the direct asymmetric aldol reactions catalyzed by aldolase enzymes and antibodies have been reported.[11] List, Barbas, and their co-workers have explored asymmetric aldol reactions with excellent enantioselectivities using L-proline[12–15] and structural analogues[16] for α-branched aliphatic aldehydes. Only fair ee's were observed for the reaction of aromatic aldehydes with acetone promoted by L-proline or its derivatives and structural analogues,[17] with the exception of N-substituted L-prolinamide derivatives.[18,19] L-Prolinamide derivatives from β-amino alcohols gave high ee's for *p*-substituted benzaldehydes.

Although homogeneous catalysts are desirable because of their high activities and selectivities, the separation of homogeneous catalysts from the products of the reaction and/or recovery of the catalysts are problems inherent with conventional catalysts. Heterogeneous catalysis has advantages, such as easy separations and efficient recycling and minimization of metal traces in the product. Solid supported proline-terminated peptides, polystyrene and benzyl pencillin derivatives in conjunction with proline grafted

* Corresponding author. Tel./fax: +91 40 2716 0921.
E-mail address: mlakshmi@iict.res.in (M. L. Kantam).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.12.119

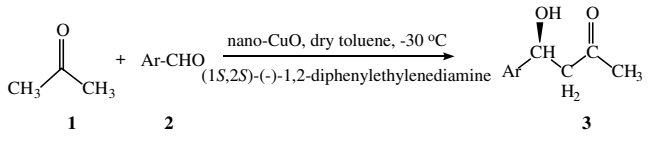
into mesoporous MCM-41 provided moderate ee's for the direct asymmetric aldol reaction.[20] L-Proline in ionic liquids and silica-supported ionic liquids also provided moderate enantioselectivity.[21,22]

Remarkable success in the direct asymmetric aldol reaction was achieved with the introduction of in situ prepared heterobimetallic catalysts, composed of both Lewis acidic sites and Lewis/Bronsted basic sites.[23] Evans et al. and other groups have explored asymmetric direct enolate–electrophile reactions catalyzed by Mg and derived complexes.[24,25]

Nanocrystalline metal oxides find excellent applications as active adsorbents for gases and the destruction of hazardous chemicals,[26,27] and as catalysts for various organic transformations.[28,29] Recently, we reported asymmetric epoxidation, Henry, Michael addition, and direct asymmetric aldol reactions using nanocrystalline MgO[30,31] and asymmetric hydrosilylation using nanocrystalline CuO.[32]

We report herein direct asymmetric aldol reactions of aromatic aldehydes with acetone using nanocrystalline copper(II) oxide to afford optically active β-hydroxy carbonyl compounds in good yields and good to moderate ee's (Scheme 1).

We initially studied the direct asymmetric aldol reaction of *p*-nitrobenzaldehyde (**2a**) with acetone (**1**) using nano-CuO in the presence of different chiral ligands and the results are summarized in Table 1. It is important to note that diphenylethylenediamine ligands were crucial for the catalytic activity of nano-CuO in terms of both yield and ee (Table 1, entries 1 and 2). The use of diphosphine ligands gave higher yields but poor ee's were obtained. Moreover, the bidentate oxygen-based ligand BINOL produced only trace amounts of the product despite a prolonged reaction time.



1 2 3

Scheme 1. Direct asymmetric aldol reactions of aromatic aldehydes with acetone using nanocrystalline copper(II) oxide.

The asymmetric aldol reaction between **1** and **2a** in the presence of (1*S*,2*S*)-(−)-diphenylethylenediamine with commercial CuO afforded a 38% yield of the desired product with 4% ee at room temperature. Nano-CuO with a higher surface area (136 m^2/g) and smaller crystal size (7–9 nm)[33] than commercial CuO (SA: 1.952 m^2/g) displayed higher activity. The higher enantioselectivity correlated to the smaller crystal size, which complexes effectively with the chiral ligand.

In the process of optimization of the reaction conditions, we explored the use of different solvents and different temperatures (Table 2).

From Table 2 it is evident that toluene is the best solvent in terms of both yield and ee. A significant increase in ee was observed by decreasing the reaction temperature. The solvent toluene and a temperature of −30 °C resulted in optimum enantioselectivity. When the reaction was conducted with 0.050 g of catalyst, the aldol product was obtained in low yield in a longer reaction time, but no change in ee was observed (Table 2, entry 7).

Cordova et al. reported that α-amino acids, β-amino acids, and chiral amines containing a primary amine functionality catalyze the direct asymmetric intermolecular aldol reaction with high enantioselectivities.[34] To evaluate the importance of our catalytic system, we carried out the aldol reaction with (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine (20 mol %), 1 mmol of **2a**, and 1 mL of **1** in the absence of nano-CuO at room temperature. The aldol adduct (**3a**) was formed in 20% yield and the ee was 0%. When the reaction was conducted in the absence of both

Table 1
The effect of the ligand on the asymmetric aldol reaction between **1** and **2a** catalyzed by nano-CuO at room temperature[a]

Entry	Ligand	Time (h)	Yield[b] (%)	ee[c] (%)
1	(1*R*,2*R*)-(+)-1,2-Diphenylethylenediamine	6	92	(*S*)[d] 18
2	(1*S*,2*S*)-(−)-1,2-Diphenylethylenediamine	6	92, 38[e]	(*R*)[d] 25, 4[e]
3	(1*R*,2*R*)-(−)-1,2-Diaminocyclohexane	6	90	0
4	(1*S*,2*S*)-(+)-1,2-Diaminocyclohexane	6	90	4
5	(*S*)-(−)-1,1′-Binaphthyl-2-2′-diamine	6	88	0
6	(*R*)-(−)-1,1′-Binaphthyl-2-2′-diamine	6	88	0
7	(*R*)-BINAP	6	92	0
8	(*S*)-BINAP	6	92	5
9	(*R*)-(−)-BINOL	24	Trace	0
10	(*S*)-(−)-BINOL	24	Trace	0
11	(+)-Diethyl-L-tartrate	24	No reaction	—
12	(−)-Diethyl-L-tartrate	24	No reaction	—
13	[*R*(*R**,*R**)]-(+)-2,2′-Isopropylidenebis (4-benzyl-2-oxazoline)	36	No reaction	—
14	2,2′-Isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline]	36	No reaction	—

[a] Reaction conditions: **2a** (1.0 mmol), **1** (13.7 mmol), nano-CuO (0.150 g), dry toluene (3 mL), ligand (0.02 mmol).
[b] Isolated yields.
[c] The % ee was determined by HPLC analysis using a chiral column (Chiralpak AS-H).
[d] Absolute configurations were assigned by comparison of the sign of specific rotations relative to the literature values.
[e] Using commercial CuO.

Table 2
The effect of solvent and temperature on the asymmetric aldol reaction between **1** and **2a** catalyzed by nano-CuO in the presence of (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine as chiral ligand[a]

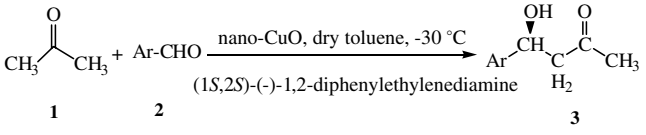
Entry	Solvent	Temp (°C)	Time (h)	Yield[b] (%)	ee[c]
1	THF	25	6	62	5
2	DMSO	25	6	60	0
3	$CHCl_3$	25	6	5	0
4	Acetone	25	6	80	0
5	Acetone	−30	24	65	0
6	Toluene	25	6	92	25
7	Toluene	0	6	85	38
8	Toluene	−30	24	80	72
9[d]	Toluene	−30	48	55	72

[a] Reaction conditions: **2a** (1.0 mmol), **1** (13.7 mmol), (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine (0.02 mmol), nano-CuO(0.150 g), solvent (3 mL).
[b] Isolated yields.
[c] The % ee was determined by HPLC analysis using a chiral column (Chiralpak AS-H).
[d] Using nano-CuO (0.050 g).

the catalyst and the chiral auxiliary, no product was obtained even after a long reaction time. Nano-CuO was tested in the direct asymmetric aldol reaction of various substituted aromatic and heteroaromatic aldehydes (Table 3).

The nano-CuO catalyst could be reused for four cycles without loss of activity and selectivity. No reaction occurred when the reaction was conducted with the filtrate obtained after removal of the solid catalyst. This supported the observation that the active catalyst species did not leach from the solid catalyst. The absence of copper in the filtrate was also confirmed by AAS studies. The X-ray powder diffraction patterns of fresh and used nano-CuO did not differ in the range $2\theta = 0$–$80°$, which confirmed the fact that the structure and morphology of the catalyst remained the same during the course of the reaction.

Table 3
Direct asymmetric aldol reaction of aromatic aldehydes and acetone with nano-CuO[a]



1 **2** **3**

Entry	Ar	Product	Time (h)	Yield[b] (%)	ee[c] (%)
1	(**2a**) 4-NO_2-C_6H_4	**3a**	24	80, 75[d]	72, 70[d]
2	(**2b**) 4-Cl-C_6H_4	**3b**	24	75	66
3	(**2c**) 4-Br-C_6H_4	**3c**	24	78	70
4	(**2d**) 4-CN-C_6H_4	**3d**	24	70	64
5	(**2e**) 4-F-C_6H_4	**3e**	24	80	66
6	(**2f**) 2-NO_2-C_6H_4	**3f**	24	70	64
7	(**2g**) 3-NO_2-C_6H_4	**3g**	24	70	34
8	(**2h**) C_6H_5	**3h**	24	60	66
9	(**2i**) 4-CH_3-C_6H_4	**3i**	36	50	62
10	(**2j**) 2-Pyridyl	**3j**	36	70	28
11	(**2k**) 2-Naphthyl	**3k**	24	80	75

[a] All reactions were performed on 1 mmol of substrate in 1 mL (13.7 mmol) of acetone using 150 mg of nano-CuO in dry toluene (3 mL).
[b] Isolated yields.
[c] The % ee was determined by HPLC analysis using a chiral column (Chiralpak AS-H, OJ-H).
[d] Fourth cycle.

In conclusion, nano-CuO is an active, reusable catalyst for the production of chiral β-hydroxy carbonyl compounds through direct asymmetric aldol reaction with good yields and good to moderate enantioselectivities in the presence of (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine.

A typical procedure: A mixture of **1** (1 mL, 13.7 mmol), (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine (0.02 mmol, 45 mg) and a catalyst (150 mg) was introduced into a 25 mL round-bottomed flask containing dry toluene (3 mL) at −30°C and stirred for 30 min under a nitrogen atmosphere. To the reaction mixture, aldehyde (1 mmol) was added at that temperature and stirring was continued. After completion of the reaction (monitored by TLC), the reaction mixture was centrifuged to separate the catalyst and was washed several times with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. After purification by column chromatography on silica gel using 10% ethyl acetate in petroleum ether, the aldol adduct was obtained. The (1*S*,2*S*)-(−)-1,2-diphenyl ethylenediamine can be recovered quantitatively with no observable change in enantiomeric purity from the same chromatographic column by increasing the proportion of ethyl acetate in the eluent.

Acknowledgments

T.R. thanks UGC and LCP thanks CSIR, New Delhi, for the award of senior research fellowships. Nanocrystalline metal oxide samples were obtained from Nanoscale Materials Inc., Manhattan, KS 66502, USA.

References and notes

1. Marciniak, G.; Delgado, A.; Velly, J.; Leclerc, G.; Decker, N.; Schwartz, J. *J. Med. Chem.* **1989**, *32*, 1402.
2. Enders, D.; Muller, S.; Demir, A. S. *Tetrahedron Lett.* **1988**, *29*, 6437.
3. Trost, B. M. *Science* **1991**, *254*, 1471.
4. Palomo, C.; Oiarbide, M.; Garcia, J. *Chem. Soc. Rev.* **2004**, *33*, 65.
5. Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352.
6. Shibasaki, M. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; Vol. 11, Chapter 6, p 197.
7. Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 1871.
8. Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168.
9. Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003.
10. Evans, D. A.; Downey, C. W.; Hubbs, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 8706.
11. Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352.
12. List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395.
13. Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260 and references cited therein.

14. Pidathala, C.; Hoang, L.; Vognola, N.; List, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 2785.
15. Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580.
16. Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983.
17. Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, *37*, 570.
18. Tang, Z.; Jiang, F.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 5262.
19. Tang, Z.; Yang, Z.-H.; Chen, X. H.; Cun, L. F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285.
20. Andreae, M. R. M.; Davis, A. P. *Tetrahedron: Asymmetry* **2005**, *16*, 2487.
21. Loh, T.-P.; Feng, L.-C.; Yang, H.-Y.; Yang, J.-Y. *Tetrahedron Lett.* **2002**, *43*, 8741.
22. Chandrasekhar, S.; Narsimhulu, Ch.; Ramakrishna, N.; Sultana, S. *Tetrahedron Lett.* **2004**, *45*, 4581.
23. For reviews, see: Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 1236.
24. Evans, D. A.; Nelson, S. G. *J. Am. Chem. Soc.* **1997**, *119*, 6452.
25. Willis, M. C.; Cutting, G. A.; Piccio, V. J.-D.; Durbin, M. J.; John, M. P. *Angew. Chem. Int., Ed.* **2005**, *44*, 1543.
26. Itoh, H.; Utamapanya, S.; Stark, J. V.; Klabunde, K. J.; Schlup, K. J. *Chem. Mater.* **1993**, *5*, 71.
27. Jiang, Y.; Decker, S.; Mohs, C.; Klabunde, K. J. *J. Catal.* **1998**, *180*, 24.
28. Sun, N.; Klabunde, K. J. *J. Catal.* **1999**, *185*, 506.
29. Choudary, B. M.; Mulukutla, R. S.; Klabunde, K. J. *J. Am. Chem. Soc.* **2003**, *125*, 2020.
30. Choudary, B. M.; Kantam, M. L.; Ranganath, K. V. S.; Mahendar, K.; Sreedhar, B. *J. Am. Chem. Soc.* **2004**, *126*, 3396.
31. Choudary, B. M.; Chakrapani, L.; Ramani, T.; Vijay Kumar, K.; Lakshmi Kantam, M. *Tetrahedron* **2006**, *62*, 9571.
32. Lakshmi Kantam, M.; Laha, S.; Yadav, J.; Likhar, P. R.; Sreedhar, B.; Choudary, B. M. *Adv. Synth. Catal.* **2007**, *349*, 1797.
33. Carnes, C. L.; Stipp, J.; Klabunde, K. J. *Langmuir* **2002**, *18*, 1352.
34. Córdova, A.; Zou, W.; Dziedzic, P.; Ibrahem, I.; Reyes, E.; Xu, Y. *Chem. Eur. J.* **2006**, *12*, 5383.