Enantioselective nitroaldol (Henry) reaction using copper(II) complexes of (−)-sparteine†

H. Maheswaran,*[a] K. Leon Prasanth,[a] G. Gopi Krishna,[a] K. Ravikumar,[b] B. Sridhar[b] and M. Lakshmi Kantam[a]

The dichloro[(−)-sparteine-N,N']copper(II) complex provides Henry adducts with high enantioselectivities (73–97% ee) in Henry reaction between nitromethane and various aldehydes.

The Henry reaction constitutes a fundamental carbon–carbon bond forming reaction in organic chemistry, which has been used for the construction of numerous useful compounds.[1] The nitro group of these products can undergo the Nef reaction,[2] reduction to an amino group, or nucleophilic displacement.[3] The catalytic asymmetric Henry reaction (AH reaction) has been successfully implemented only in a very few cases. For example, the AH reactions with impressive enantioselectivity are realized using heterobimetallic catalysts (rare earth–lithium–BINOL complexes),[4] dinuclear zinc chiral semi-azacrown complexes,[5] chiral bisoxazoline copper(II) complexes,[6] and zinc–chiral (+)-N-methyl ephedrine complexes.[7] In this communication, we report a new catalytic protocol for the AH reaction using divalent copper complexes derived from quinolizidine alkaloid (−)-sparteine. The impact of sparteine as a chiral ligand in asymmetric synthesis, particularly in organolithium chemistry, has been incredible and, more recently, the use has been extended to other metal ions such as Mg, Pd, Zn, and Cu.[8]
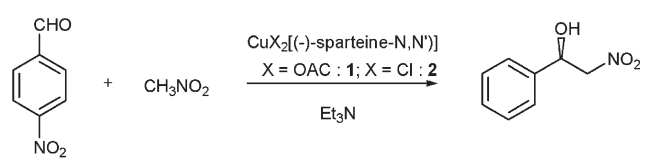
The most interesting aspect of copper(II) complexes with (−)-sparteine is present in their configurational and conformational features. For example, the structure of divalent [(−)-sparteine-N,N']copper(II) complex in solid-state[9] and in solution[10] has indicated that the copper atom in this complex is four-coordinate, and has distorted tetrahedral geometry.[11] The formation of the complex leads to a conversion of the nitrogen atom configuration in the sparteine ligand; as a consequence, all the four alkaloid rings adopt chair conformations, and configuration at the A/B and C/D ring junctions are *trans* and *cis*, respectively.[9,12] This conformation differs from that of free (−)-sparteine ligand, in which the C-ring takes the boat form, and the configuration at the C/D ring-junction is *trans*.[13] This stereochemical outcome in the copper(II) complex is precisely due to sterically demanding fused rings of sparteine.[9–13] Thus, the formation of (−)-sparteine complexes in which tertiary diamine acts as a bidentate ligand demands a very precise stereochemical conditions. This invariably makes the

structure of the complexes semi-rigid, stereochemically well defined, and conformationally less flexible.[14]

Two different copper(II) complexes of (−)-sparteine were synthesized by following a procedure described previously;[9,10] they are namely, diacetatato[(−)-sparteine-N,N']copper(II) (**1**), and dichloro[(−)-sparteine-N,N']copper(II) (**2**). These complexes in crystalline form were then screened as catalysts for the AH reaction between 4-nitrobenzaldehyde and nitromethane in various solvents at ambient temperature. Table 1 presents some representative results from the screening.

Catalyst **1** directly catalyzes the Henry reaction with nitromethane, and affords excellent yields of the Henry adducts in a variety of solvents, without requiring base promoters such as triethylamine (entries 1–4). Apparently, Lewis acidic copper(II)

Table 1 Screening of reaction parameters for the reaction of nitromethane with 4-nitrobenzaldehyde using copper(II)-(−)-sparteine complexes[a]

Entry	Catalyst	Solvent	Et$_3$N (mol%)[b]	Temp/°C	Time/h	Yield (%)[c]	ee (%)[d]
1	**1**	DCM	0	35	20	>95	<4 (R)
2	**1**	DMF	0	35	20	>95	<4 (R)
3	**1**	THF	0	35	20	>95	<4 (R)
4	**1**	MeOH	0	35	20	>95	<4 (R)
5	**2**	DCM	0	35	48	<5	nd
6	**2**	DCM	3	35	24	82	<4 (R)
7	**2**	DMF	0	35	24	33	37 (R)
8	**2**	DMF	1.5	35	24	70	33 (R)
9	**2**	DMF	3	35	10	95	16 (R)
10	**2**	MeOH	0	35	48	<5	nd
11	**2**	MeOH	1.5	35	20	50	57 (R)
12	**2**	MeOH	3	35	12	90	73 (R)
13	**2**	MeOH	4.5	35	07	95	60 (R)
14	**2**	MeOH	6	35	04	95	49 (R)
15	**2**	MeOH	3	0	18	90	86 (R)

[a] All reactions were performed on a 0.5 mmol scale with 20 mol% of catalyst and 2.0 equiv. of nitromethane in 1 mL solvent at the indicated temperature. [b] Amount of Et$_3$N is expressed in mol% relative to aldehyde substrate. [c] Values are isolated yields after chromatographic purification. [d] Enantiomeric excess (ee) was determined by HPLC using Chiralcel OD-H column using isopropanol and hexane; the absolute configuration (R-isomer or S-isomer) of the Henry adduct was assigned by comparison with optical rotation data of known compound.[4a,6a,18]

[a]IPC Division, Indian Institute of Chemical Technology, Hyderabad, India. E-mail: maheswaran_dr@yahoo.com; Fax: 91 4027160921; Tel: 91 4027193510
[b]X-ray Crystallography Centre, Indian Institute of Chemical Technology, Hyderabad, India

† Electronic supplementary information (ESI) available: Synthesis and characterization of complexes **1** and **2**, reaction procedure, NMR, and HPLC data for Henry adducts. See DOI: 10.1039/b610203d

complex **1** bearing moderately charged acetate anions facilitate deprotonation of nitromethane as a prelude to the aldol addition process.[6a] Nevertheless, this reaction was nonstereoselective because very poor ee values (<4%) for nitroaldol products were obtained (entries 1–4). Similar results were obtained when other aromatic aldehydes such as benzaldehyde, 4-chlorobenzaldehyde, and 4-methoxybenzaldehyde were evaluated under similar reaction conditions.

In contrast, when catalyst **2** was screened under similar conditions, Henry reaction proceeded in a sluggish manner and gave very poor yields in the solvents studied; <5% conversion in dichloromethane and methanol, and 33% in DMF (entries 5, 7, and 10). Base promoters such as triethylamine significantly increase both the speed and the yield of this reaction (entries 5–15); thus, catalyst **2** could only be activated toward the Henry reaction under double catalytic activation (DCA) conditions.[15] Surprisingly, excellent ee values up to 73–86% were obtained for the Henry adducts in methanol (entries 12,15). Moreover, the degree of chiral induction observed with **2** depends not only on the nature of the solvent used but also on the quantity of triethylamine base used (see Table 1). For example, both dichloromethane and DMF were very poor solvents for the catalytic AH reaction as low ee values were obtained (entries 6, 8–9). In fact, increase in the amount of triethylamine base lowers the enantioselectivity of the nitroaldol product from 33% to 16% in DMF (entries 6–8). Methanol is the best solvent for the catalytic AH reaction when catalyst **2** was used in combination with triethylamine. Increasing the amount of triethylamine also results in a drop in ee values (entries 10–14); however the optimum amount of triethylamine that is needed to achieve good conversion (90%) and enantioselectivity (73%) at 35 °C is 3 mol% relative to the substrate (entry 12). As the temperature decreases, ee increases remarkably with a decrease in the rate of reaction. At 0 °C, the AH reaction between 4-nitrobenzaldehyde and nitromethane gave 86% ee for the Henry adduct (entry 15).

With optimised conditions in hand, the scope of the reaction was explored (Table 2). In general, high enantiomeric excesses (73–97% ee) are observed at 0 °C for aromatic aldehydes bearing either electron-withdrawing or electron-donating groups (entries 1–8). In particular, the aromatic aldehydes bearing substituents in the *ortho* position, gave high enantioselectivities (entries 3, 5, 7). The reason for this appears to be more steric in nature because *ortho* substituents that are incapable of chelation to a metal (example: Cl) also gave excellent enantioselectivity (entry 7). Aliphatic cyclic, branched or unbranched aldehydes are also acceptable substrates, affording nitroaldol adducts in good yields and enantioselectivities (entries 9–12, 78–90% ee).

A root-mean-square (r.m.s.) overlay of Cu, and N atoms (r.m.s. deviation = 0.012 Å) of X-ray structures of both catalysts **1** and **2** are presented in Fig. 1.[9,16] It is very clear that the conformations of the (−)-sparteine ligands are nearly identical in both the complexes as a very good r.m.s. fit was obtained. However, these structures differ widely in the relative orientation of their counter anions; as a consequence, significant differences in the bond angles and torsion angles (15 to 20 degrees) around the copper(II) site were observed.[9] X-ray analysis also showed the copper(II) site is distorted in both the complexes, however, such a distortion is much more severe in catalyst **2** than in catalyst **1**.[9,17] Both ESR and optical spectral studies on **2** strongly indicate that the solid-state coordination

Table 2 Asymmetric Henry reaction of nitromethane with various aldehydes catalyzed by dichloro[(−)-sparteine-*N,N'*]copper(II) (**2**)[a]

RCHO + CH₃NO₂ → (with CuCl₂[(−)-sparteine-N,N'] (20-mol%), MeOH ; Et₃N (3 mol%), 0°C) → R-CH(OH)-CH₂-NO₂

1 **2** **3a-3l**

R = C₆H₅ ; **1a**
R = 4-NO₂-C₆H₄ ; **1b**
R = 2-NO₂-C₆H₄ ; **1c**
R = 4-MeO-C₆H₄ ; **1d**
R = 2-MeO-C₆H₄ ; **1e**
R = 4-Cl-C₆H₄ ; **1f**
R = 2-Cl-C₆H₄ ; **1g**

R = 1-naphthyl ; **1h**
R = cyclohexyl ; **1i**
R = ⁿbutyl ; **1j**
R = Isobutyl ; **1k**
R = ⁿpropyl ; **1l**

Entry	Substrate	Product	Time/h	Yield (%)[b]	ee (%)[c]
1	**1a**	**3a**	12	>95	79 (R)
2	**1b**	**3b**	18	90	86 (R)
3	**1c**	**3c**	14	80	89 (R)
4	**1d**	**3d**	11	>95	80 (R)
5	**1e**	**3e**	07	>95	97 (R)
6	**1f**	**3f**	16	80	81 (R)
7	**1g**	**3g**	24	60	96 (R)
8	**1h**	**3h**	24	82	73 (R)
9	**1i**	**3i**	24	85	85 (R)
10	**1j**	**3j**	24	78	78 (R)
11	**1k**	**3k**	24	80	90 (R)
12	**1l**	**3l**	24	84	81 (R)

[a] All reactions were performed on a 0.5 mmol scale with 20 mol% of catalyst, triethylamine (3 mol% relative to aldehyde), and 2.0 equiv. of nitromethane in 1 mL methanol at 0 °C. [b] Values are isolated yields after chromatographic purification. [c] Enantiomeric excess (ee) was determined by HPLC using Chiralcel OD-H, OJ-H, or AD columns using isopropanol and hexanes; the absolute configuration (*R*-isomer or *S*-isomer) of the Henry products were assigned by comparison with optical rotation data of known compounds.[4a,6a,18]
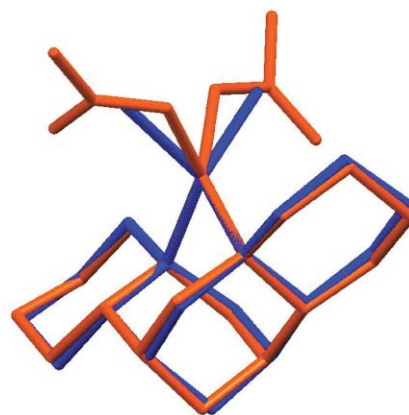

Fig. 1 An r.m.s. overlay of Cu, and N atoms (r.m.s. deviation = 0.012 Å) from X-ray structures of **1** (red) and **2** (blue).[21]

environment around the copper(II) site is retained in the solution-state as well.[10b] Thus, the nature of the copper(II) site differs widely from each other even though ligand conformation is retained in these complexes. These differences may partly explain the differences that are experimentally observed in their catalytic activities and selectivities in the asymmetric Henry reaction.

In conclusion, we have shown that dichloro[(−)-sparteine-*N,N'*]copper(II) is an effective catalyst for asymmetric Henry reaction of nitromethane with various structurally divergent aldehydes. In general, high enantioselectivities were obtained for

most of the substrates, particularly, when reaction is carried out under DCA conditions with Et_3N base in methanol. The chemistry offered here will certainly be useful due to ready availability of (−)-sparteine as well as the (+)-sparteine surrogate as well. Further studies focussed on exploring the use of copper(II)-(−)-sparteine complexes for other asymmetric reactions are in progress.

Notes and references

1 For recent reviews, see: (a) F. A. Luzio, *Tetrahedron*, 2001, **57**, 915–945; (b) N. Ono, *The Nitro group in Organic Synthesis*, Wiley-VCH, New York, 2001; (c) D. Seebach, A. K. Beck, T. Mukhopadhyay and E. Thomas, *Helv. Chim. Acta*, 1982, **65**, 1101–1133.

2 (a) M. Yamaguchi, T. Shiraishi and M. Hirama, *J. Org. Chem.*, 1996, **61**, 3520; (b) M. Yamaguchi, Y. Igarashi, R. S. Reddy, T. Shiraishi and M. Hirama, *Tetrahedron*, 1997, **53**, 11223.

3 (a) R. Breslow, *Science*, 1982, **218**, 532; (b) A. J. Kirby, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 707.

4 (a) H. Sasai, T. Suzuki, S. Arai and M. Shibasaki, *J. Am. Chem. Soc.*, 1992, **114**, 4418–4420; (b) M. Shibasaki and N. Yoshikawa, *Chem. Rev.*, 2002, **102**, 2187–2209.

5 (a) B. M. Trost and V. S. C. Yeh, *Angew. Chem., Int. Ed.*, 2002, **41**, 861–863; (b) B. M. Trost, V. S. C. Yeh, H. Ito and N. Bremeyer, *Org. Lett.*, 2002, **4**, 2621–2623.

6 (a) D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw and C. W. Downey, *J. Am. Chem. Soc.*, 2003, **125**, 12692–12693; (b) C. Christensen, K. Juhl, R. G. Hazell and K. A. Jørgensen, *J. Org. Chem.*, 2002, **67**, 4875; (c) Da.-M. Du, S.-F. Lu, T. Fang and J. Xu, *J. Org. Chem.*, 2005, **70**, 3712–3715.

7 C. Palomo, M. Oiarbide and A. Laso, *Angew. Chem., Int. Ed.*, 2005, **44**, 3881–3884.

8 D. Hoppe and O. Zschage, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 69; (b) D. Hoppe, in *Topics in Organometallic Chemistry*, ed. D. M. Hodgson, Springer, Heidelberg, 2003, vol. 5, 61; (c) S. T. Kerrick and P. Beak, *J. Am. Chem. Soc.*, 1991, **113**, 9708; (d) D. R. Jensen, J. S. Pugsley and M. S. Sigman, *J. Am. Chem. Soc.*, 2001, **123**, 7475; (e) E. M. Ferreira and B. M. Stoltz, *J. Am. Chem. Soc.*, 2001, **123**, 7725; (f) S. Kiyooka, Y. Takeshita, Y. Tanaka, T. Higaki and Y. Wada, *Tetrahedron Lett.*, 2006, **47**, 4453–4456; (g) R. Shintani and G. C. Fu, *Angew. Chem., Int. Ed.*, 2002, **41**, 1057; (h) Yu. Zhang, S.-M. Yeung, H. Wu, D. P. Heller, C. Wu and W. D. Wulff, *Org. Lett.*, 2003, **5**, 1813–1816; (i) J. Zhu, N. P. Grigoriadis, J. P. Lee and J. A. Porco, Jr., *J. Am. Chem. Soc.*, 2005, **127**, 9342–9343; (j) K. Sorger, H. Petersen and J. Stohrer, *US Patent*, 2005, 6,924,386.

9 (a) Y.-M. Lee, G. Chung, Mi.-A. Kwon and S. N. Choi, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 2000, **56**, 67–68; (b) S. Lopez, I. Muravyov, S. R. Pulley and S. W. Keller, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1998, **54**, 355–357.

10 (a) E. Boschmann, L. M. Weinstock and M. Carmack, *Inorg. Chem.*, 1974, **13**, 1297; (b) Y. M. Lee, Mi.-A. Kwon, S. K. Kang, J. H. Jeong and S.-N. Choi, *Inorg. Chem. Commun.*, 2003, **6**, 197–201.

11 Four-coordinate Cu(II) complexes exhibit a strong tendency toward square-planar geometries; not tetrahedral geometry, see: B. J. Hathaway, in *Comprehensive Coordination Chemistry*, ed. G. Wilkinson, Pergamon Press, New York, 1987, vol. 5, ch. 53.

12 (a) B. Jasiewicz, E. Sikorska, I. V. Khmelinskii, B. Warzajtis, U. Rychlewska, Wł. Boczon and M. Sikorski, *J. Mol. Struct.*, 2004, **707**, 89–96; (b) G. Schroeder, W. Wysocka, B. Łeska, R. Kolanos, K. Eitner and J. K. Przybylak, *J. Mol. Struct.*, 2002, **616**, 193–199.

13 (a) T. Borowiak and I. Wolska, *J. Mol. Struct.*, 1995, **374**, 97; (b) W. Wysocka and T. Brukwicki, *J. Mol. Struct.*, 1996, **385**, 23.

14 (a) V. Galasso, F. Asaro, F. Berti, B. Kovac, I. Habuš and A. Sacchetti, *Chem. Phys.*, 2003, **294**, 155–169; (b) W. Boczon, *Heterocycles*, 1992, **33**, 1101; (c) K. B. Wiberg and W. F. Bailey, *Angew. Chem., Int. Ed.*, 2000, **39**, 2127–2129.

15 S. Kanemasa and K. Ito, *Eur. J. Org. Chem.*, 2004, 4741–4753.

16 The r.m.s. overlay of X-ray structures (**1** and **2**) was obtained by calculations involving published X-ray crystal structure data (see ref. 9) using Mercury software; for further details see: I. Bruno, J. J. C. Cole, P. R. Edgington, M. K. Kessler, C. F. Macrae, P. McCabe, J. Pearson and R. Taylor, *Acta Crystallogr., Sect. B: Struct. Sci.*, 2002, **58**, 389–397.

17 The X-ray structure (see ref. 9) reveals a distorted tetrahedral copper center for **1** and **2**. The CuN2, CuX2 bond angles are 90.1°, 90.5° and 92.4°, 106.9° for **1** and **2**, respectively. The degree of distortion from the planarity reflected by the magnitude of the dihedral angle between the CuN2 plane and CuX2 plane, which is 45.8° and 67.0° for **1** and **2**, respectively.

18 (a) M. Watanabe, K. Murata and T. Ikariya, *J. Org. Chem.*, 2002, **67**, 1712; (b) B. M. Trost and V. S. C. Yeh, *Angew. Chem., Int. Ed.*, 2002, **41**, 861; (c) B. M. Choudary, K. V. S. Ranganath, U. Pal, M. L. Kantam and B. Sreedhar, *J. Am. Chem. Soc.*, 2005, **127**, 13167–13171.