

## Enantioselective turnover in glyoxylate-ene reactions catalyzed by chiral copper complexes

Manoj K. Pandey, Alakesh Bisai and Vinod K. Singh\*

Department of Chemistry, Indian Institute of Technology, Kanpur 208 016, India

Received 3 November 2005; revised 22 November 2005; accepted 30 November 2005

Available online 19 December 2005

**Abstract**—The catalytic, enantioselective carbonyl-ene reaction of ethyl glyoxylate with  $\alpha$ -methylstyrene and 4-halo- $\alpha$ -methylstyrene has been investigated in the presence of copper triflate–bisoxazoline complexes. The reaction proceeded smoothly to give  $\gamma,\delta$ -unsaturated- $\alpha$ -hydroxy esters in moderate to good yields and with excellent enantioselectivity (up to 100% ee). A hypothesis has been provided to explain the reversal of enantioselectivity in the reaction.

© 2005 Elsevier Ltd. All rights reserved.

The enantioselective carbonyl-ene reaction promoted by a catalytic amount of chiral Lewis acid is an excellent route to optically active homoallylic alcohols.<sup>1</sup> Among many variants of this reaction, the glyoxylate-ene reaction is of particular significance as it provides chiral  $\alpha$ -hydroxy esters, which have great synthetic importance. While Whitesell described the first asymmetric carbonyl-ene reaction using auxiliary based glyoxylate,<sup>2</sup> the first example of a catalytic enantioselective ene reaction was reported by Yamamoto and co-workers.<sup>3</sup> This led to a flurry of activity in this area where major advances have been made by Mikami,<sup>4</sup> Evans<sup>5</sup> and others.<sup>6–8</sup> Excellent enantioselectivity has been achieved mainly with two types of ligands, the Ti complex of BINOL and  $C_2$ -symmetric Cu(II) complex of bis(oxazolinyl) (box) ligands **1** (Fig. 1). The sense of asymmetric induction for the glyoxylate-ene reaction catalyzed by the Cu(II) complex of **1a** (SbF<sub>6</sub> as the counter anion) was opposite to that of the Cu(II) complex of **1b** (OTf as the counter anion).<sup>5</sup> This mode of enantioselective turnover was first observed by Jørgensen who ascribed

the reversal to a change in the metal centre geometry from square planar (for **1a**) to tetrahedral (for **1b**).<sup>6a,c</sup> However, this proposal has not been accepted in the absence of any credible evidence. It has been argued that due to the high barrier for square planar to tetrahedral distortion for four coordinate Cu(2+) complexes, intervention of the latter geometry is less unlikely.<sup>5a</sup> However, it is believed that geometrical change does occur, but it is quite flexible in nature.<sup>6c</sup> In this letter, we describe our efforts in this area and report a high level of enantioselectivity in the glyoxylate-ene reaction using other chiral ligands. We also provide our analysis on the proposed model to explain the reversal in the enantioselectivity.

Earlier we reported the synthesis and application of chiral pyridine bis(diphenyloxazoline)–copper complexes in the enantioselective allylic oxidation of olefins<sup>9</sup> and cyclopropanation reactions.<sup>10</sup> Since these pybox ligands have not been used for glyoxylate-ene reactions, it was worthwhile to try them in the first instance. The Cu(II)

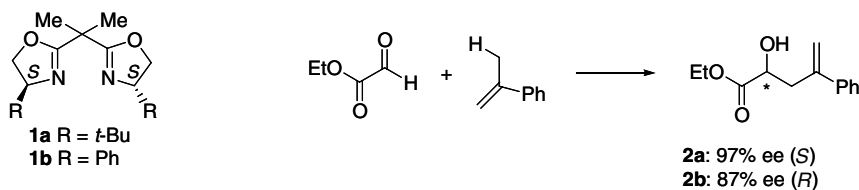


Figure 1. Glyoxylate-ene reaction.

\* Corresponding author. Tel.: +91 512 2597291; fax: +91 512 2597436; e-mail: [vinodks@iitk.ac.in](mailto:vinodks@iitk.ac.in)

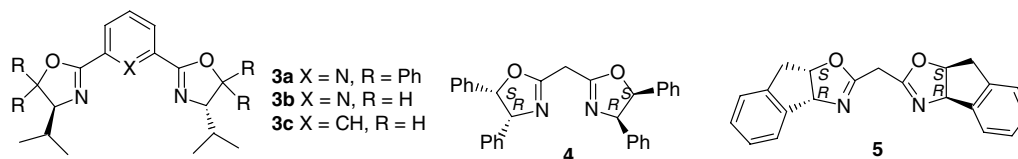


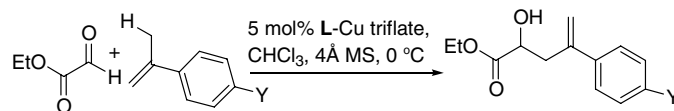
Figure 2.

complex of the ligands **3** (Fig. 2) catalyzed the reaction of ethyl glyoxylate and  $\alpha$ -methylstyrene to give **2a**, but there was virtually no asymmetric induction in the reaction (up to 2% ee). Next, we investigated ligands possessing structures similar to that of the box ligands **1a** and **1b** but with conformational rigidity in the substituents at the chiral centres. Bisoxazolines **4**<sup>11</sup> and **5**<sup>12</sup> are such chiral ligands where there is bisoxazoline rigidity due to the inherent structure (Fig. 2).

At the outset, the glyoxylate-ene reaction was carried out at 0 °C in different solvents using 5 mol % of chiral ligand **4** and Cu(OTf)<sub>2</sub> in the presence of 4 Å molecular sieves. The chemical yield of **2a** remained almost the same (38–50%), however, the enantioselectivity varied greatly for each solvent; toluene (72% ee), DCM (79.2% ee), CHCl<sub>3</sub> (93.5% ee), hexane (43.2% ee), ether (87% ee), DCE (12% ee), CCl<sub>4</sub> (63% ee). In view of the high optical yield in chloroform, it was chosen as the preferred solvent. Since 4 Å molecular sieves enhanced the enantioselectivity in the above reaction by 4–5%, it was used in all subsequent reactions. The ene reaction of ethyl glyoxylate with  $\alpha$ -methylstyrene and 4-halo- $\alpha$ -methylstyrenes was studied with 5 mol % of Cu(II) and Cu(I) complexes (triflate as the counter anion) of the chiral ligands **4** and **5** under the above conditions and the results are reported in Table 1. In the case of  $\alpha$ -methylstyrene, a maximum of 93.5% ee for the product **2a** was obtained using the complex of Cu(OTf)<sub>2</sub> and the chiral ligand **4** as catalyst (entry 1). The enantioselectivity dropped to 88.6% on the use of (CuOTf)<sub>2</sub>·Tol (entry 2). A similar trend in the enantioselectivity was obtained in the case of 4-fluoro- $\alpha$ -methylstyrene (entries 3 and 4). 4-Chloro- $\alpha$ -methylstyrene gave the ene product in 100% ee using the Cu(II) complex and 90.8% ee using the

Cu(I) complex as catalysts (entries 5 and 6). In all the above cases using **4** as the chiral ligand, the absolute stereochemistry of the product was *S*. The glyoxylate-ene reaction was also carried out using the chiral ligand **5** and the results are summarized in Table 1. A maximum ee of 70.5% for **2a** was obtained using the Cu(II) complex of ligand **5** (entry 7). In virtually all the cases, the trend in the enantioselectivity with Cu(II) and Cu(I) complexes was similar but the sense of asymmetric induction was opposite (entries 7–12).

The observed enantioselectivity in the above ene reaction catalyzed by copper complexes of ligands **4** and **5** can be rationalized via the transition state models proposed in Figure 3. It is proposed that the ligand **4** and ethyl glyoxylate forms a tetrahedral complex with Cu(OTf)<sub>2</sub>. Although four-coordinate Cu(II) complexes prefer square planar geometry, the driving force for the tetrahedral geometry in this case is the  $\pi$ - $\pi$  stacking of one of the phenyl groups on the left hand side and the carbonyl moiety of the glyoxylate. Since the distance between the phenyl and carbonyl groups is between 3 and 3.5 Å, there might be some attractive interaction, which would stabilize this tetrahedral geometry. Thus, the *Re* face of the aldehyde is blocked by the phenyl ring and the reaction is promoted from the *Si* face of the coordinated aldehyde. The results from entries 2, 4 and 6 of Table 1 indicate that the reaction was equally feasible with the Cu(I) complex of ligand **4**. Since tetrahedral geometry is more favorable in the case of Cu(I) complexes, it is obvious that the same transition state model operates to provide the same sense of asymmetric induction in the reaction. The reversal in the enantioselectivity with the chiral ligand **5** is typical and can be explained using a square planar geometry model, which is usually

Table 1. Glyoxylate-ene reaction catalyzed by Cu complexes of chiral ligands **4** and **5**

Entry	Y	L-Cu triflate	Time (h)	Yield (%)	% ee
1	H	<b>4</b> -Cu(II)	4	46	93.5 ( <i>S</i> )
2	H	<b>4</b> -Cu(I)	4	38	88.6 ( <i>S</i> )
3	F	<b>4</b> -Cu(II)	3	31	91.2 ( <i>S</i> )
4	F	<b>4</b> -Cu(I)	4	32	87.7 ( <i>S</i> )
5	Cl	<b>4</b> -Cu(II)	4	32	100 ( <i>S</i> )
6	Cl	<b>4</b> -Cu(I)	5	34	90.8 ( <i>S</i> )
7	H	<b>5</b> -Cu(II)	5	64	70.5 ( <i>R</i> )
8	H	<b>5</b> -Cu(I)	4	51	42.0 ( <i>R</i> )
9	F	<b>5</b> -Cu(II)	3	40	51.8 ( <i>R</i> )
10	F	<b>5</b> -Cu(I)	8	42	56.6 ( <i>R</i> )
11	Cl	<b>5</b> -Cu(II)	4	42	68.3 ( <i>R</i> )
12	Cl	<b>5</b> -Cu(I)	5	30	65.4 ( <i>R</i> )

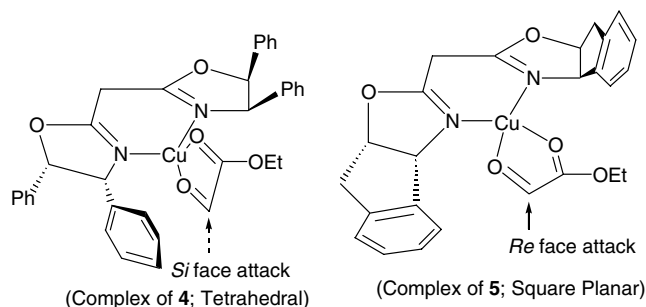


Figure 3. Stereochemical model for the glyoxylate-ene reaction.

more favorable in the case of Cu(II) complexes.<sup>13</sup> There is no extra stabilization, as proposed in the case of **4**, for change over in the metal geometry from square planar to tetrahedral. Thus, the glyoxylate-ene reaction with the Cu(II) complex of chiral ligand **5** proceeds via normal square planar geometry where the reaction occurs from the *Re* face of the coordinated aldehyde. The lower enantioselectivity in the case of ligand **5** is manifest from the transition state model. As a result of the ring fusion at the chiral centres, the fused aryl ring moves away from the aldehyde, thus making the *Si* face of the coordinated aldehyde vulnerable to attack to some extent. The Cu(I) complex of the ligand **5** gave the same sense of induction (entries 8, 10 and 12) as that of the Cu(II) complex. This can be explained by invoking octahedral geometry where two solvent ligands could be assumed to chelate the copper.

In conclusion, we have shown that ligands **4** and **5** gave high enantioselectivity in the glyoxylate-ene reaction. A maximum of 100% ee was obtained in this reaction.<sup>14</sup> We have also provided a hypothesis to explain the reversal in enantioselectivity in the reaction. The results reported here also support the proposition of Jørgensen for change over in metal geometry to account for the reversal in enantioselectivity.

General procedure for the enantioselective glyoxylate-ene reaction. A mixture of chiral ligand **4** or **5** (0.015 mmol, 6 mol %), (CuOTf)<sub>2</sub>-toluene or Cu(OTf)<sub>2</sub> (0.0125 mmol, 5 mol %) and 4 Å powdered molecular sieves (50 mg) in chloroform (2.0 mL) was stirred at room temperature for 1.5 h. Then, the reaction mixture was cooled to 0 °C and treated with ethyl glyoxylate (0.25 mmol) followed by  $\alpha$ -methylstyrene (0.375 mmol). The resulting mixture was stirred for 3–8 h at the same temperature. After the reaction was complete (monitoring with TLC), most of the solvent was removed under reduced pressure and the crude mixture was purified by column chromatography to give the pure ene product (Table 1).

#### Acknowledgements

We thank the Department of Science and Technology, India, for a research grant. A.B. thanks the Council of Scientific and Industrial Research, New Delhi, for a senior research fellowship.

#### References and notes

- For a review on enantioselective carbonyl-ene reactions, see: (a) Mikami, K.; Terada, M.; Narisawa, S.; Nakai, T. *Synlett* **1992**, 255–265; (b) Berrisford, D. J.; Bolm, C. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1717–1719; (c) Dias, L. C. *Curr. Org. Chem.* **2000**, *4*, 305–342.
- Whitesell, J. K.; Bhattacharya, A.; Buchanan, C. M.; Chen, H. H.; Deyo, D.; James, D.; Liu, C.-L.; Minto, M. A. *Tetrahedron* **1986**, *42*, 2993–3001.
- Maruoka, K.; Hoshino, Y.; Shirasaka, T.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 3967–3970.
- (a) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949–3954; (b) Mikami, K. *Pure Appl. Chem.* **1996**, *68*, 639–644; (c) Mikami, K.; Matsukawa, S. *Nature* **1997**, *385*, 613–615.
- (a) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824–5825; (b) Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936–7943.
- (a) Johannsen, M.; Jørgensen, K. A. *J. Org. Chem.* **1995**, *60*, 5757–5762; (b) Carreira, E. M.; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 3649–3650; (c) Chavarot, M.; Byrne, J. J.; Chavant, P. Y.; Pardillos-Guindet, J.; Vallee, Y. *Tetrahedron: Asymmetry* **1998**, *9*, 3889–3894; (d) Manickam, G.; Sundarajan, G. *Tetrahedron: Asymmetry* **1999**, *10*, 2913–2925; (e) Thorhaug, J.; Roberson, M.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2002**, *8*, 1888–1898.
- For some recent papers in the area, see: (a) Pandiaraju, S.; Chen, G.; Lough, A.; Yudin, A. K. *J. Am. Chem. Soc.* **2001**, *123*, 3850–3851; (b) Kaden, S.; Hiersemann, M. *Synlett* **2002**, 1999–2002; (c) Kezuka, S.; Ikeno, T.; Yamada, T. *Org. Lett.* **2001**, *3*, 1937–1939; (d) Sekiguti, T.; Lizuka, Y.; Takizawa, S.; Jayaprakash, D.; Arai, T.; Sasai, H. *Org. Lett.* **2003**, *5*, 2647–2650; (e) Kezuka, S.; Kogami, Y.; Ikeno, T.; Yamada, T. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 49–58; (f) Simonelli, B.; Orlandi, S.; Benglia, M.; Pozzi, G. *Eur. J. Org. Chem.* **2004**, 2669–2673; (g) Takizawa, S.; Somei, H.; Jayaprakash, D.; Sasai, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5711–5714; (h) Yuan, Y.; Zhang, X.; Ding, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 5478–5480; (i) Guo, H.; Wang, X.; Ding, K. *Tetrahedron Lett.* **2004**, *45*, 2009–2012; (j) Mandoli, A.; Orlandi, S.; Pini, D.; Salvadori, P. *Tetrahedron: Asymmetry* **2004**, *15*, 3233–3244; (k) Caplan, N. A.; Hancock, F. E.; Page, P. C. B.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1685–1688; (l) Langer, M.; Remy, P.; Bolm, C. *Synlett* **2005**, 781–784.
- For mechanistic aspects of the reaction, see: Morao, I.; McNamara, J. P.; Hiller, I. H. *J. Am. Chem. Soc.* **2003**, *125*, 628–629.
- (a) DattaGupta, A.; Singh, V. K. *Tetrahedron Lett.* **1996**, *37*, 2633–2636; (b) Sekar, G.; DattaGupta, A.; Singh, V. K. *J. Org. Chem.* **1998**, *63*, 2961–2967.
- DattaGupta, A.; Bhuniya, D.; Singh, V. K. *Tetrahedron* **1994**, *50*, 13725–13730.
- For the application of chiral ligand **4** in other enantioselective reactions, see: (a) Bernardi, L.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5772–5773; (b) Hong, S.; Tian, S.; Metz, M. V.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 14768–14783; (c) Christensen, C.; Juhl, K.; Jørgensen, K. A. *Chem. Commun.* **2001**, 2222–2223; (d) Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, *32*, 7373–7376.
- For applications of chiral ligand **5** in other enantioselective reactions, see: (a) Saito, T.; Yamada, T.; Miyazaki, S.; Otani, T. *Tetrahedron Lett.* **2004**, *45*, 9581–9584; (b) Bandini, M.; Bernardi, F.; Bottoni, A.; Cozzi, P. G.;

- Miscione, G. P.; Umani-Ronchi, A. *Eur. J. Org. Chem.* **2003**, 2972–2984; (c) Zhang, X.; Qu, Z.; Ma, Z.; Shi, W.; Jin, X.; Wang, J. *J. Org. Chem.* **2002**, 67, 5621–5625; (d) Rechavi, D.; Lemaire, M. *Org. Lett.* **2001**, 3, 2493–2496; (e) Ghosh, A. K.; Shirai, M. *Tetrahedron Lett.* **2001**, 42, 6231–6233; (f) Bandini, M.; Cozzi, P. G.; Negro, L.; Umani-Ronchi, A. *Chem. Commun.* **1999**, 39–40; (g) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1996**, 37, 3815–3818.
13. For an X-ray structure of the hydrated complex of **1** with a Cu salt, see: Evans, D. A.; Johnson, J. S.; Burgey, C. S.; Campos, K. R. *Tetrahedron Lett.* **1999**, 40, 2879–2882.
  14. The enantiomeric excess in all the cases was determined by HPLC (Chiralcel OD-H and Chiralpak AD-H columns).