C_2-Symmetric Copper(II) Complexes as Chiral Lewis Acids. Enantioselective Catalysis of the Glyoxylate−Ene Reaction

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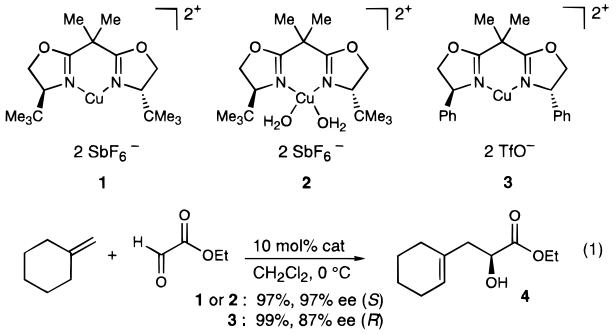
The development of enantioselective Lewis acid catalyzed carbonyl addition reactions of π-nucleophiles such as enolsilanes and allylstannanes is a topic of current interest.[1] The extension of this general process to include simple olefinic nucleophiles via the carbonyl−ene reaction[2] has important practical implications. In this context, Mikami and Nakai have reported a catalytic enantioselective ene reaction with glyoxylate esters;[3] however, due to the limiting reactivity of the catalyst−glyoxylate complex,[4] only nucleophilic 1,1-disubstituted olefins may be employed. We have recently reported that bidentate bis(oxazolinyl) (box) Cu(II) complexes **1**−**3** are effective enantioselective catalysts in Diels−Alder[5] and aldol reactions[6] with substrates that can participate in catalyst chelation. In this study, we demonstrate that



these chiral Cu(II)-based Lewis acids also catalyze the enantioselective addition of a variety of olefins to glyoxylate esters[7] to provide α-hydroxy esters, versatile synthons in organic synthesis. The greater reactivity of these catalysts significantly extends the scope of this process.

Initial experiments revealed that [Cu((*S*,*S*)-*t*-Bu-box)]$(SbF_6)_2$ complex (**1**)[5c] (10 mol %, CH_2Cl_2, 0 °C) promotes the addition of methylenecyclohexane to ethyl glyoxylate (eq 1) to afford (*S*)-**4** in high enantioselectivity and yield (97% ee, 0 °C, <3 h, 97% yield). In addition, we prepared the bis(aquo) complex [Cu((*S*,*S*)-*t*-Bu-box)$(H_2O)_2$]$(SbF_6)_2$ (**2**), a blue solid that is readily obtained from solutions of **1** exposed to water.[8] This complex is an equally effective catalyst with only a slight decrease in reaction rate relative to the anhydro complex **1** (eq 1, 97% ee, 0 °C, <6 h, 97%). Concurrently, it was discovered that the [Cu((*S*,*S*)-Ph-box)]$(OTf)_2$ complex (**3**) is also an excellent catalyst for this reaction (eq 1, 87% ee, 0 °C, 99% yield);[9] however, the absolute stereochemistry of the resulting product (*R*)-**4** is the opposite to that produced by (*S*,*S*)-*t*-Bu-box catalysts **1** and **2** (vide infra). Accordingly, either enantiomer of **4** may be obtained from a single enantiomeric ligand series.

The practical advantages associated with the use of the bis(aquo) Cu(II)-box complex **2**, as a readily prepared bench-stable solid, prompted us to select this catalyst for development. The reaction of ethyl glyoxylate with methylenecyclohexane (eq 1) catalyzed by **2** was found to proceed with catalyst loadings as low as 0.1 mol % without significant loss in enantioselectivity or yield (CH_2Cl_2, 0 °C, 24 h, ≥90% yield, 94% ee). This reaction may also be conducted in other solvents such as toluene and diethyl ether with no loss in enantioselectivity.

The scope of the reaction of ethyl glyoxylate with other olefins has been investigated (Table 1). The *t*-Bu-box complex **2** (1 mol %, CH_2Cl_2, 0 °C) afforded excellent enantioselectivities and yields in the reactions of ethyl glyoxylate with isobutylene (**5**: 96% ee), α-methylstyrene (**6**: 93% ee), and methylenecyclopentane (**7**: 96% ee).[10] Catalyst **3** (10 mol %, CH_2Cl_2, 0 °C) also provided the corresponding (*R*) α-hydroxy esters with good to excellent enantiocontrol and yield (**5**, 92% ee; **6**, 89% ee; **7**, 76% ee).

The box−Cu(II) complexes can also be employed to catalyze additions of unsymmetrical 1,1-disubstituted olefins to ethyl glyoxylate. To realize a regioselective process in this reaction the catalyst must be capable of discriminating between methyl and methylene groups at the two possible reaction centers. The addition of 2-methyl-1-heptene to ethyl glyoxylate catalyzed by **2** proceeds with excellent enantioselectivity to yield (*S*)-**8** (96% ee); however, the regioselectivity is only 74:26. In contrast, the (*S*)-Ph-box-derived catalyst **3** mediates the process with superior regioselectivity (90:10) while maintaining high enantioselectivity to provide the enantiomeric adduct (*R*)-**8** (91% ee). In previous studies, this level of regioselectivity has not been obtained with this enophile.[2,3] Functionalized 1,1-disubstituted olefins, such as silyl and benzyl-protected methallyl alcohol derivatives, also react with ethyl glyoxylate in the presence of the Cu(II) catalysts to yield **9** and **10**, respectively, uncontaminated by regioisomeric byproducts.

(1) For leading references, see: (a) Bach, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 417−419. (b) Duthaler, R. O.; Hafner, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 43−45. (c) For a comprehensive review of catalytic enantioselective aldol reactions, see: Nelson, S. G. *Tetrahedron*: *Asymmetry* **1998**, *9*, 357−389.

(2) For a general review of enantioselective ene reactions, see: (a) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021−1050. Yamamoto has also reported a catalytic ene reaction with 1,1-disubstituted olefins: (b) Mauruoka, K.; Hoshino, Y.; Shirasaka, T.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 3967−3970. Chiral glyoxylate esters in ene reactions: (c) 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.

(3) (a) Mikami, K. *Pure Appl. Chem.* **1996**, *68*, 639−644. (b) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949−3954.

(4) The structure of neither the active BINOLTiCl_2 catalyst nor its glyoxylate complex is known; however, recent speculation on the latter structure has appeared: Corey, E. J.; Barnes-Seeman, D.; Lee, T. W.; Goodman, S. N. *Tetrahedron Lett.* **1997**, *38*, 6513−6516 and references therein.

(5) (a) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460−6461. (b) Evans, D. A.; Lectka, T.; Miller, S. J. *Tetrahedron Lett.* **1993**, *34*, 7027−7030. (c) Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798−800. (d) Evans, D. A.; Johnson, J. S. *J. Org. Chem.* **1997**, *62*, 786−787.

(6) (a) Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814−5815. (b) Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893−7894. For Sn(II)−box complexes as aldol catalysts, see: (c) Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859−10860.

(7) For hetero Diels−Alder reactions employing glyoxylate esters and metal−box complexes, see: (a) Johannsen, M.; Jørgensen, K. A. *J. Org. Chem.* **1995**, *60*, 5757−5762. (b) Ghosh, A. K.; Mathivanan, P.; Cappiello, J.; Krishnan, K. *Tetrahedron*: *Asymmetry* **1996**, *7*, 2165−2168. (c) Johannsen, M.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1183−1185.

(8) The X-ray structure of complex **2** reveals a distorted square planar copper center. The two H_2O−Cu−N−C dihedral angles are 30.0° and 36.0°. The full details of this structure will be reported elsewhere.

(9) Other box−Cu(II) complexes afforded lower enantioselectivity: [Cu(*t*-Bu-box)]$(OTf)_2$ (86% ee), [Cu(*i*-Pr-box)]$(OTf)_2$ (19% ee), [Cu(Bn-box)]$(OTf)_2$ (2% ee), [Cu(*i*-Pr-box)]$(SbF_6)_2$ (36% ee), [Cu(Bn-box)]$(SbF_6)_2$ (23% ee), [Cu(Ph-box)]$(SbF_6)_2$ (70% ee).

(10) In a representative procedure the catalyst solution (**1** or **3**) (0.05−0.005 mmol in 1.5 mL of CH_2Cl_2) is added in one portion to the olefin (0.50 mmol) and ethyl glyoxylate (3−10 equiv) at the indicated temperature (0 or 25 °C). After the reaction has proceeded to completion (1−48 h), the mixture is directly loaded onto a 2 × 6 cm silica gel flash column and eluted with hexanes/ethyl acetate to provide the α-hydroxy ester. With catalyst **2**, the same procedure is employed except that **2** is added as a solid to a solution of olefin and glyoxylate (1.5 mL of CH_2Cl_2).

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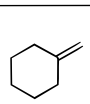
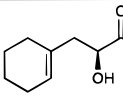
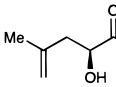
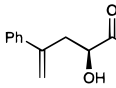
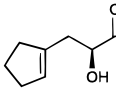
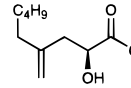
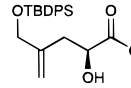
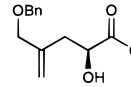
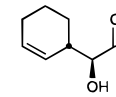
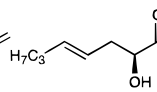
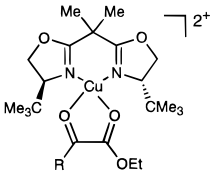
Table 1. Catalyzed Enantioselective Ene Reactions between Ethyl Glyoxylate and Representative Olefins

olefin	product[a]	cat (mol%)	T,°C	yield,%[b]	% ee[c]
	 **4**	**2** (1) **3** (10)	0	90 99	97 (*S*) 87 (*R*)
	 **5**	**2** (1) **3** (10)	0	83 92	96 (*S*) 92 (*R*)
	 **6**	**2** (1) **3** (10)	0	97 99	93 (*S*) 89 (*R*)
	 **7**	**2** (1) **3** (10)	0	95 97	96 (*S*) 76 (*R*)
	 **8**	**2** (1) **3** (10)	25	89[d] 81[e]	96 (*S*) 91 (*R*)
	 **9**	**2** (1) **3** (10)	25	72[f] 85[f]	96 (*S*) 91 (*R*)
	 **10**	**2** (10) **3** (2)	25	62[f] 88[f]	98 (*S*) 92 (*R*)
	 **11**	**1** (10) **3** (10)	0	95[g] 70[h]	98 (*S*) 94 (*R*)
	 **12**	**1** (10)	25	96[i]	98 (*S*)

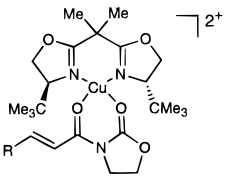
[a] Absolute configurations assigned by conversion to the MTPA esters (Supporting Information). [b] Isolated yields. [c] Enantiomeric excess determined by GLC (Cyclodex-β column) or HPLC (Chiralcel OD-H column). [d] 74:26 regioselectivity. [e] 90:10 regioselectivity. [f] Only regioisomer isolated. [g] *endo*:*exo* 86:14. [h] *endo*:*exo* 95:5. [i] *E*:*Z* 96:4.

Asymmetric ene reactions with significantly less nucleophilic monosubstituted and 1,2-disubstituted olefins have not been previously rendered catalytic. However, in the presence of 10 mol % of the anhydrous Cu(II) complexes **1** and **3**, cyclohexene underwent reaction with ethyl glyoxylate (10 equiv) to provide the α-hydroxy ester **11** in high enantioselectivity (Table 1, **1**: (*S*)-**11** 98% ee; **3**: (*R*)-**11** 94% ee).[11] It appears that the observed reaction diastereoselectivity is ligand-dependent since the Ph-box complex **3** again exhibits greater selectivity than the *tert*-Bu-box catalyst (**1**: *endo*:*exo* 86:14; **3**: *endo*:*exo* 95:5).[12] The less nucleophilic 1-hexene is also a viable partner in this reaction with catalyst **1**, to yield ethyl (*S*)-2-hydroxy-4-octenoate (**12**) in 98% ee with excellent (*E*) olefin selectivity (96:4).[11] To demonstrate the preparative utility of this methodology, the reaction of ethyl glyoxylate with methylenecyclohexane was conducted on a 25-mmol scale employing 0.2 mol % (43 mg) of the box catalyst **2** to generate the desired adduct **4** (4.3 g) in high yield and enantioselectivity (86%, 97% ee).

The sense of asymmetric induction observed for reactions catalyzed by the [Cu((*S*,*S*)-*t*-Bu-box)]$(SbF_6)_2$ complex (**1**) and its bis(aquo) counterpart **2** is consistent with the intervention of a square planar catalyst−glyoxylate complex **13a**[13] in direct analogy to the related pyruvate complex **13b** previously proposed.[6b] By



13a, R = H; **13b**, R = Me



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inspection, it is evident that the *Re* face of the coordinated aldehyde in **13a** is encumbered by the *tert*-butyl substituent thus promoting reactions with olefins from the accessible aldehyde *Si* face. This catalyst architecture also accommodates the stereochemical outcome of our previously reported Diels−Alder reactions that have been proposed to proceed through the catalyst−dienophile complex **14**.[5a] In contrast, this model does not account for the sense of induction that is observed with the analogous [Cu((*S*,*S*)-Ph-box)]$(OTf)_2$ complex (**3**), an observation that might signal the intervention of an alternate metal center geometry. In view of the high barrier for the square planar → tetrahedral distortion for four-coordinate Cu(2+) complexes,[14] the intervention of four-coordinate, tetrahedral Cu(2+)−substrate complexes is unlikely;[7a] however, trigonal pyramidal four-coordinate Cu(2+) geometries do occur with some frequency.[15]

In summary, Cu(II)−box complexes are highly selective catalysts for the glyoxylate−ene reaction. The results disclosed herein considerably extend the scope of this reaction.

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Supporting Information Available: Experimental procedures for ligand synthesis, the preparation of complexes **1**−**3**, spectral data for all compounds, and stereochemical proofs (24 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

Noted Added in Proof: An example of glyoxylate−ene reaction, catalyzed by (phenylbis(oxazolinyl)Cu$(OTf)_2$, has recently been reported: Gao, Y.; Lane-Bell, P.; Vederas, J. C. *J. Org. Chem.* **1998**, *63*, 2133−2143.

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(11) A slower reaction and a reduced yield is observed when **2** is employed.

(12) The relative stereochemistry in **11** was determined by X-ray crystallography on the derived (*S*)-α-methylbenzylamide.

(13) Four-coordinate Cu(II) complexes exhibit a strong tendency toward square planar geometries, see: Hathaway, B. J. In *Comprehensive Coordination Chemistry*, Wilkinson, G. Ed.; Pergamon Press: New York,.; 1987; Vol. 5, Chapter 53.

(14) (a) Wilcox, D. E.; Porras, A. G.; Hwang, Y. T.; Lerch, K.; Winkler, M. E.; Solomon, E. I. *J. Am. Chem. Soc.* **1985**, *107*, 4015−4027. (b) Solomon, E. I.; *Comments Inorg. Chem.* **1984**, *3*, 227−320.

(15) Cambridge Structural Database survey: 134 square planar structures; 22 trigonal pyramidal structures; 3 tetrahedral structures (http://sulfur.scs.uiuc.edu/gifs/cuii.htm).