C_2-Symmetric Copper(II) Complexes as Chiral Lewis Acids. Catalytic Enantioselective Carbonyl−Ene Reactions with Glyoxylate and Pyruvate Esters

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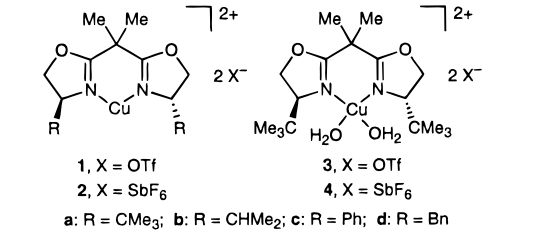
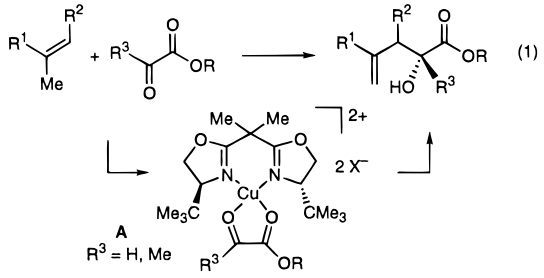
Received March 14, 2000

Abstract: The C_2-symmetric complexes [Cu(*S*,*S*)-*tert*-butylbis(oxazolinyl)]$(SbF_6)_2$ (**2a**), its bis(aquo) counterpart [Cu(*S*,*S*)-*tert*-butylbis(oxazolinyl)$(H_2O)_2$]$(SbF_6)_2$ (**4**), and [Cu(*S*,*S*)-phenylbis(oxazolinyl)]$(OTf)_2$ (**1c**) have been shown to catalyze the enantioselective ene reaction between glyoxylate esters and various olefins. Monosubstituted, disubstituted, and trisubstituted olefins each react with ethyl glyoxylate in the presence of 0.2−10 mol % of catalysts **1**, **2**, and **4** to afford the ene products in good yield and enantioselectivity. Complex **2a** has also been shown to catalyze the addition of 1,1-disubstituted olefins to methyl pyruvate in good yields (76−95%) and excellent enantioselectivies (≥98% ee). The synthetic utility of the glyoxylate−ene reaction was demonstrated by conversion of the resulting α-hydroxy ester into the corresponding methyl ester, free acid, Weinreb amide, and α-azido ester, all with no detectable racemization.

Introduction

The carbonyl−ene reaction is an important carbon−carbon bond forming process. As a consequence, the development of enantioselective variants of this reaction is a topic of ongoing interest,[1] and both chiral auxiliary-based[2] and catalytic[3,4] versions have been reported. The glyoxylate and pyruvate variants of this reaction (eq 1, R^3 = H, Me) afford α-hydroxy esters, versatile synthons in organic synthesis.[5] The objective of this research effort has been to investigate the utility of the chiral bis(oxazolinyl) (box) Cu(II) complexes **1**−**4** as Lewis acid catalysts in the enantioselective carbonyl−ene reaction with α-dicarbonyl substrates. Prior studies from our laboratory had provided the precedent that one might expect the illustrated catalyst−substrate complex **A** (R^3 = H, Me) would exhibit good facial discrimination in this process.





Prior Art. Major advances in the development of chiral auxiliary based enantioselective carbonyl−ene reaction variants have been reported by Whitesell.[2] Glyoxylate esters derived from 8-phenylmenthol react with a broad variety of olefins to afford the ene products in high diastereoselectivity when promoted by $SnCl_4$ (eq 2). In another significant study, the first example of a catalytic enantioselective ene reaction was reported by Yamamoto.[3] The scope of this reaction was limited to pentafluorobenzaldehyde as the carbonyl component and nucleophilic olefins such as 2-(phenylthio)propene. More recently, Mikami and Nakai have reported a catalytic enantioselective ene reaction with glyoxylate esters.[4] While this reaction is restricted to 1,1-disubstituted olefins due to the modest Lewis acidity of the titanium−BINOL complex, the enantioselection is exceptional (eq 3). Although neither the structure of the active (BINOL)$TiCl_2$ catalyst nor its glyoxylate complex has yet been characterized, nonchelating activation of the glyoxylate has been proposed.[6] It was our expectation that the more Lewis acidic cationic Cu(II) complexes **1**−**4** might extend the scope of this process.

Cu(II) Complexes. We have recently reported that bidentate bis(oxazolinyl) (box) Cu(II) complexes **1**−**4** are effective

(1) For a general review of enantioselective ene reactions see: (a) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021−1050. (b) Dias, L. C. *Curr. Org. Chem.* **2000**, *4*, 305−342.

(2) 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 and references therein. Reaction between *N*-glyoxyloyl-(2*R*)-borane-10,2-sultam and monosubstituted olefins has also been reported: Jezewski, A.; Chajewska, K.; Wielogórski, Z.; Jurczak, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1741−1749.

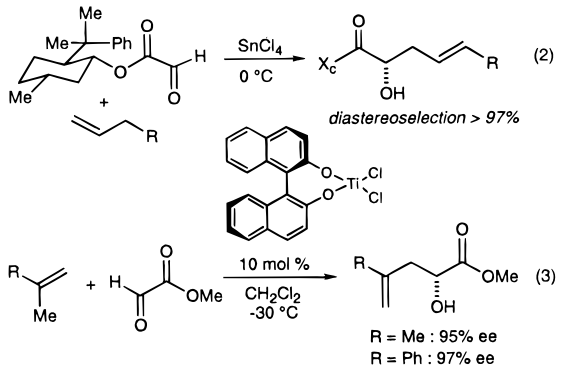
(3) Mauruoka, K.; Hoshino, Y.; Shirasaka, T.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 3967−3970.

(4) (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.

(5) Coppola, G. M.; Schuster, H. F. α-*Hydroxy Acids in Enantioselective Syntheses*; VCH: Weinheim, 1997.

(6) Corey, E. J.; Barnes-Seeman, D.; Lee, T. W.; Goodman, S. N. *Tetrahedron Lett.* **1997**, *38*, 6513−6516 and references therein.

10.1021/ja000913t CCC: $19.00 © 2000 American Chemical Society
Published on Web 08/04/2000

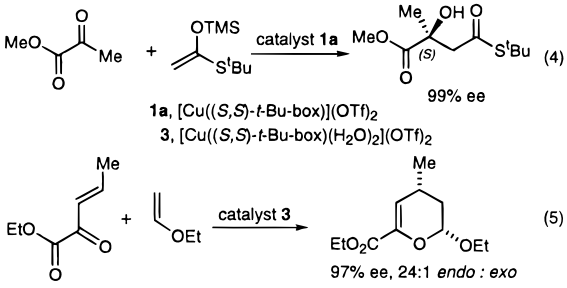


(2)

(3)

enantioselective catalysts in the Diels−Alder,[7] aldol,[8] Michael,[9] and amination[10] reactions.[11] In all of these processes, substrate−catalyst chelation has afforded high levels of asymmetric induction and predictable models for chirality transfer. The cationic Cu(II) complexes such as [Cu(*S*,*S*)-*tert*-butylbis(oxazolinyl)]$(SbF_6)_2$ (**2a**), are also considerably more Lewis acidic than the general family of titanium(IV)-based Lewis acids, $[Ti(OR)_2]Cl_2$, that have been used as ene and Diels−Alder reaction catalysts.

Those reactions involving chelate activation of α-dicarbonyl substrates by the Cu(II)-box catalyst (e.g. **A**, eq 1) are particularly relevant to the present investigation. Aldol reactions of pyruvate esters[8c,d] (eq 4) and hetero-Diels−Alder reactions of β,γ-unsaturated α-keto esters[7h] (eq 5) both proceed in



(4)

(5)

excellent enantioselectivity in the presence of Cu(II)-box catalysts. Catalyst−substrate complexes **5a** and **5b** have been implicated as the species responsible for the observed enantioselection (Figure 1). It is noteworthy that ene byproducts have been observed in hetero-Diels−Alder reactions employing glyoxylate esters and Cu(II)-box complexes.[12] In the following discussion, we demonstrate that these chiral complexes also catalyze the enantioselective addition of a variety of olefins to glyoxylate and pyruvate esters.[13]

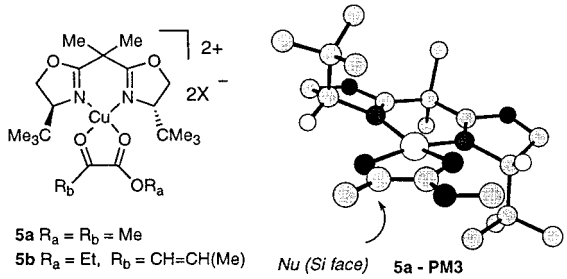
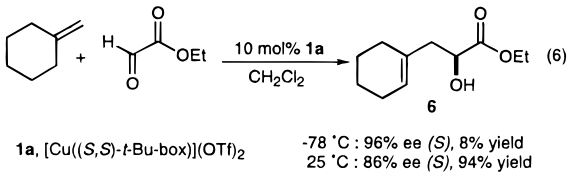


Figure 1. Calculated PM3 structure of [Cu((*S*,*S*)-*t*-Bu-box)(pyruvate)]$^{2+}$.

Ene Reactions of Glyoxylate Esters

A preliminary evaluation of the ene reaction between methylenecyclohexane and ethyl glyoxylate at −78 °C revealed that [Cu((*S*,*S*)-*t*-Bu-box)]$(OTf)_2$ (**1a**) promoted a highly selective ene process; however, no catalyst turnover was observed. When the reaction temperature was increased to 25 °C, the process became catalytic in metal complex **1a** with only modest loss of enantioselectivity (eq 6). On the basis of this lead, this process was employed for reaction optimization.



(6)

Reaction Optimization. Various Cu(II)-box complexes and counterions were examined in the reaction of methylene cyclohexane and ethyl glyoxylate (Table 1). The [Cu((*S*,*S*)-*t*-Bu-box)]$(SbF_6)_2$ complex **2a** exhibited high reactivity affording the ene products in excellent enantioselectivity. While the [Cu((*S*,*S*)-Ph-box)]$(OTf)_2$ complex **1c** is also an excellent catalyst for this reaction, the absolute stereochemistry of the resulting product (*R*)-**6** is opposite to that produced by (*S*,*S*)-*t*-Bu-box catalysts **1a** and **2a** (vide infra). Accordingly, either enantiomer of **6** may be obtained from a single enantiomeric ligand series.

The bis(aquo) complex [Cu((*S*,*S*)-*t*-Bu-box)$(H_2O)_2$]$(SbF_6)_2$ (**4**), a bench-stable blue crystalline solid that is readily obtained from solutions of **2a** upon exposure to water, was also evaluated as a reaction catalyst.[14] This complex was also found to be an effective catalyst for this reaction with only a slight decrease in reaction rate relative to the anhydro complex **2a** (eq 7: 97%, 96% ee, 25 °C, 1 h). Due to the practical advantages of [Cu-

(7) (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.; Barnes, D. M. *Tetrahedron Lett.* **1997**, *38*, 57−58. (e) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559−7573. (f) Evans, D. A.; Johnson, J. S. *J. Org. Chem.* **1997**, *62*, 786−787. (g) Evans, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 4895−4896. (h) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635−1649.

(8) (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. (c) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Connell, B. *J. Am. Chem. Soc.* **1999**, *121*, 669−685. (d) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686−699. For Sn(II)-box complexes as aldol catalysts see: (e) Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859−10860.

(9) (a) Evans, D. A.; Willis, M. C.; Johnston, J. N. *Org. Lett.* **1999**, *1*, 865−868. (b) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994−1995.

(10) Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, 595−598.

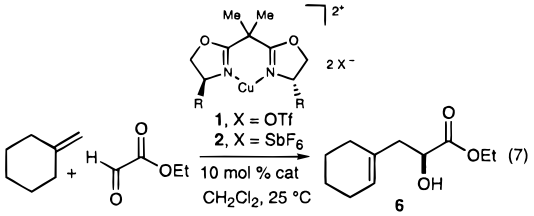
(11) For two recent reviews on various aspects of chiral Cu(2+) Lewis acid-catalyzed processes see: (a) Evans, D. A.; Rovis, T.; Johnson, J. S. *Pure Appl. Chem*, **1999**, *71*, 1407−1415. (b) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335.

(12) (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. During the course of this research two examples of Cu(II)-box catalyzed glyoxylate−ene reactions have appeared: (d) Gao, Y.; Lane-Bell, P.; Vederas, J. C. *J. Org. Chem.* **1998**, *63*, 2133−2143. (e) Gethergood, N.; Jørgensen, K. A. *J. Chem. Soc., Chem. Commun.* **1999**, 1869−1870.

(13) A preliminary account of this work has appeared: Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay; S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824−5825.

(14) The X-ray structure of complex **4** reveals a distorted square-planar copper center. The two H_2O−Cu−N−C dihedral angles are 30.0° and 36.0°. See: Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. C.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541−4544.

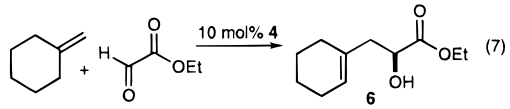
Table 1. Effect of Ligand and Counterion in the Glyoxylate−Ene Reaction (Eq 7)



entry	R-Box	X$^-$	time, h[a]	% ee[b]
1	**1c**, R=Ph	OTf	8	79 (*R*)
2	**1b**, R=CHMe$_2$	OTf	8	19 (*S*)
3	**1d**, R=Bn	OTf	8	2 (*R*)
4	**1a**, R=CMe$_3$	OTf	20	86 (*S*)
5	**2c**, R=Ph	SbF$_6$	1	70 (*R*)
6	**2b**, R=CHMe$_2$	SbF$_6$	<3	36 (*S*)
7	**2d**, R=Bn	SbF$_6$	<3	23 (*S*)
8	**2a**, R=CMe$_3$	SbF$_6$	<1	96 (*S*)

[a] Time to complete conversion. [b] Enantiomeric excess determined by GLC (Cyclodex-β column).

Table 2. Solvent and Temperature Effects in the Catalyzed Glyoxylate−Ene Reaction (Eq 7)



entry	solvent[a]	T, °C	time, h[b]	% ee[c]	% yield[d]
1	THF	25	<2	93 (*S*)	nd
2	PhCH$_3$[e]	25	<2	97 (*S*)	nd
3	Et$_2$O[e]	25	<2	97 (*S*)	nd
4	CH$_3$CN	25	nd	38 (*R*)	nd
5	CH$_2$Cl$_2$	25	<1	96 (*S*)	95
6	CH$_2$Cl$_2$	0	1	97 (*S*)	97
7	CH$_2$Cl$_2$	-30	19	99 (*S*)	93

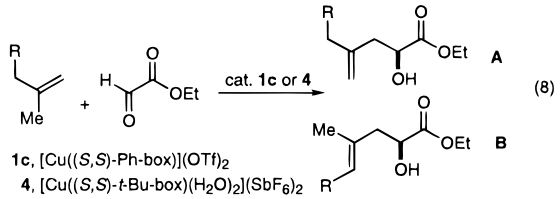
[a] All experiments were performed at 0.33 M in substrate. [b] Time to complete conversion. [c] Enantiomeric excess determined by GLC (Cyclodex-β column). [d] Isolated yields. [e] Low solubility of catalyst in this solvent. nd = not determined.

((*S*,*S*)-*t*-Bu-box)(H$_2$O)$_2$](SbF$_6$)$_2$ (**4**), optimization of the carbonyl−ene reaction parameters was investigated with this complex. Examination of various solvents in the reaction of methylenecyclohexane and ethyl glyoxylate catalyzed by complex **4** revealed that high enantioselectivities were obtained in CH_2Cl_2 (96% ee), THF (93% ee), toluene (97% ee), and diethyl ether (97% ee) (Table 2). Not unexpectedly, the use of coordinating solvents such as acetonitrile resulted in diminished enantioselectivity (38% ee (*R*)) and reaction rate. High yields and enantioselectivities could be obtained in methylene chloride over the temperature range of −30 to +25 °C (entries 5−7). While methylene chloride was chosen for subsequent studies, other reaction solvents should not be excluded.

Catalyst loading was examined using [Cu((*S*,*S*)-*t*-Bu-box)-(H$_2$O)$_2$](SbF$_6$)$_2$ (**4**) and methylenecyclohexane (Table 3). It was found that catalyst loadings as low as 0.2 mol % may be achieved (entry 5: 86%, 97% ee); however, 1.0 mol % catalyst loadings are typically used for practical reasons. The amount of glyoxylate used in the reaction was also examined (Table 3). When the amount of glyoxylate used was increased from 1.0 to 3.0 equiv, higher yields were obtained (entries 6−8). Use of 5.0 equiv of glyoxylate increased the yield to 95% (entry 9). The use of the olefin in 3-fold excess also afforded good yield and enantioselectivity (entry 10: 83%, 95% ee), and no over-addition products were observed. Unless otherwise specified, reactions were performed using 3.0 equiv of ethyl glyoxylate.

Reaction Scope. The scope of the glyoxylate reaction with other olefins was then investigated. As a class, simple 1,1-disubstituted olefins were all found to be excellent substrates (Table 4). The [Cu((*S*,*S*)-*t*-Bu-box)(H$_2$O)$_2$](SbF$_6$)$_2$ complex (**4**) afforded excellent enantioselectivities and yields in the reactions of ethyl glyoxylate with isobutylene, α-methylstyrene, and methylenecyclopentane. The [Cu((*S*,*S*)-Ph-box)](OTf)$_2$ (**1c**) complex provided the corresponding (*R*) α-hydroxy esters with good to excellent enantiocontrol and yield. Absolute configuration of each product was determined by conversion to the derived MTPA esters (Supporting Information).

The Cu(II)-box complexes may also be employed to catalyze additions of unsymmetrical 1,1-disubstituted olefins to ethyl glyoxylate. As shown in eq 8, two isomeric ene products are possible. In the demanding case of 2-methyl-1-butene, the



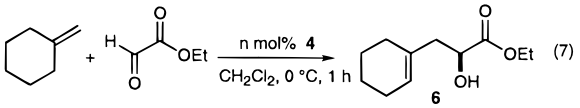
catalyst−glyoxylate complex must discriminate between a methyl and an ethyl group to effect a regioselective process. While the reaction proceeds with both [Cu((*S*,*S*)-*t*-Bu-box)-(H$_2$O)$_2$](SbF$_6$)$_2$ (**4**) and [Cu((*S*,*S*)-Ph-box)](OTf)$_2$ (**1c**) in good yields to afford **10** (90% and 84% ee, respectively), virtually no regioselection was observed in the case of catalyst **4** and only 2:1 regioselectivity was noted for catalyst **1c** (Table 5). The addition of 2-methyl-1-heptene to ethyl glyoxylate catalyzed by **4** proceeds with excellent enantioselectivity to yield (*S*)-**11** (96% ee); however, the regioselectivity is again only 3:1. In contrast, the Ph-box derived catalyst **1c** mediates the process with superior regioselectivity (90:10) while maintaining high enantioselectivity to provide the enantiomeric adduct (*R*)-**11** (91% ee). This level of regioselectivity has not been obtained with this olefin in other catalytic systems.[4]

Functionalized 1,1-disubstituted olefins, such as silyl and benzyl-protected methallyl and homomethallyl alcohol derivatives, also react with ethyl glyoxylate in the presence of the Cu(II)-box catalysts. The reaction of silyl-protected 2-methyl-2-propen-1-ol catalyzed by **4** and **1c** affords **12** in excellent enantioselectivity (96% and 91% ee, respectively) uncontaminated by regioisomeric byproducts. Yet with both **4** and **1c**, the homologue **13** is produced in relatively low enantioselectivity. The benzyl-protected 2-methyl-2-propen-1-ol is an excellent substrate for both **4** and **1c** affording **14** in high enantioselectivities (98% and 92% ee, respectively) with no regiochemical byproducts isolated. The benzyl protected homologue is also less selective in the reaction with glyoxylate, affording **15** in modest enantioselectivity and regioselectivity. The absolute configurations of the compounds illustrated in Table 5, with two exceptions, were determined via conversion to the derived MTPA esters. The configurations of compounds **13** and **15** were assigned by analogy (Supporting Information).

To date, enantioselective reactions with 1,2-disubstituted olefins have not been rendered catalytic.[15] However, in the presence of 10 mol % of the anhydrous Cu(II) complexes [Cu-((*S*,*S*)-*t*-Bu-box)(SbF$_6$)$_2$ (**2a**) and [Cu((*S*,*S*)-Ph-box)](OTf)$_2$ (**1c**), cyclohexene underwent reaction with ethyl glyoxylate (10 equiv)

(15) For chiral auxiliary based examples see: Whitesell, J. K.; Bhattacharya, A.; Aguilar, D. A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982**, 989−899.

Table 3. Effect of Catalyst Loading and Amount of Glyoxylate in the Catalyzed Glyoxylate−Ene Reaction (Eq 7)

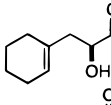
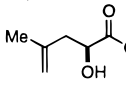
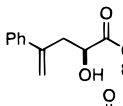
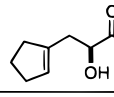


(7)

entry	mol % cat.	% ee [a]	% yield [b]	entry	mol % cat.	equiv olefin	equiv glyoxylate	% ee [a]	% yield [b]
1	10	97	96	6	1	1.0	1.0	97	52
2	5	97	97	7	1	1.0	2.0	97	86
3	2	97	90	8	1	1.0	3.0	97	90
4	1	97	90	9	1	1.0	5.0	96	95
5[c]	0.2	97	86	10[c]	1	3.0	1.0	95	83

[a] Enantiomeric excess determined by GLC (Cyclodex-β column). [b] Isolated yields. [c] Reaction time: 18 h.

Table 4. Catalyzed Enantioselective Ene Reactions between Ethyl Glyoxylate and 1,1-Disubstituted Olefins[a]

olefin	product [b]	cat (mol%)	% ee [c]	% yield [d]
	 **6**	**4** (1) **1c** (10)	97 (*S*) 87 (*R*)	90 99
	 **7**	**4** (1) **1c** (10)	96 (*S*) 92 (*R*)	83 92
	 **8**	**4** (1) **1c** (10)	93 (*S*) 89 (*R*)	97 99
	 **9**	**4** (1) **1c** (10)	96 (*S*) 76 (*R*)	95 97

[a] All reactions performed at 0.33 M in substrate in CH_2Cl_2 at 0 °C. [b] Absolute configurations assigned by conversion to the MTPA esters (Supporting Information). [c] Enantiomeric excess determined by GLC (Cyclodex-b column). [d] Isolated yields.

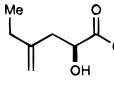
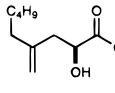
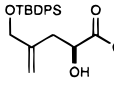
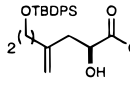
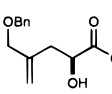
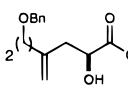
to provide the α-hydroxy ester **16** in high enantioselectivity (Table 6: 98% and 94% ee, respectively).[16] Reaction diastereoselectivity is ligand-dependent, and the Ph-box complex **1c** again exhibits greater selectivity than the *t*-Bu-box catalyst (**2a**, endo:exo 86:14; **1c**, endo:exo 95:5). The catalyzed reaction of cyclopentene with ethyl glyoxylate with **2a** afforded the ene product with excellent enantioselectivity ((*S*)-**17**; 96% ee), but only modest diastereoselectivity (endo:exo 2:1). With the Ph-box derived complex, only the more reactive SbF_6 complex **2c** could be employed to afford (*R*)-**17** in modest enantioselectivity and diastereoselectivity (78% ee, endo:exo 3:1). Both complexes **2a** and **2c** were ineffective in catalyzing the ene reaction of cycloheptene to ethyl glyoxylate to produce **18**. The addition of *cis*-2-butene[17] could be promoted by **2a** in excellent enantioselectivity to afford (*S*)-**19** but only in modest diastereoselectivity favoring the syn isomer (98% ee, anti:syn 40:60). Catalyst **2c** afforded (*R*)-**19** in good enantioselectivity and high diastereoselectivity favoring the anti isomer (90% ee, anti:syn 88:12). Complexes **2a** and **2c** were both ineffective in catalyzing the reaction with *trans*-2-butene. The absolute and relative stereochemistry of compounds **16** and **17** were determined by X-ray crystallography of the derived α-methylbenzylamide. The absolute stereochemistry of compound **19** is based on analogy. The relative stereochemistry of **19** was determined by comparison to literature data (Supporting Information).[18]

(16) A slower reaction and a reduced yield is observed when **4** is employed.

(17) Due to the volatility of *cis*-butene, the reactions were performed in sealed tubes using glyoxylate as limiting reagent (see Supporting Information).

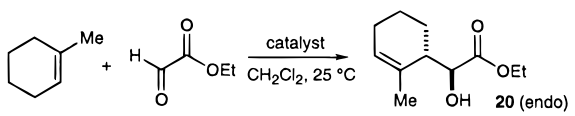
(18) Barlett, P. A.; Tanzella, D. J.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3941.

Table 5. Catalyzed Ene Reactions between Ethyl Glyoxylate and Other 1,1-Disubstituted Olefins[a]

olefin	product [b]	cat (mol%)	% ee [c]	% yield [d]	A : B [c]
	 **10**	**4** (1) **1c** (10)	84 (*S*) 90 (*R*)	78 91	55:45 67:33
	 **11**	**4** (1) **1c** (10)	96 (*S*) 91 (*R*)	89 81	60:40 98:2
	 **12**	**4** (1) **1c** (10)	96 (*S*) 91 (*R*)	72 85	>99:1 >99:1
	 **13**	**4** (1) **1c** (10)	55 (*S*) 48 (*R*)	71 75	>99:1 >99:1
	 **14**	**4** (2) **1c** (10)	98 (*S*) 92 (*R*)	62 88	>99:1 >99:1
	 **15**	**4** (1) **1c** (10)	82 (*S*) 89 (*R*)	98 98	74:26 80:20

[a] All reactions performed at 0.33 M in substrate in CH_2Cl_2 at 25 °C. [b] Absolute configurations assigned by conversion to the MTPA esters (Supporting Information). [c] Enantiomeric excess and A:B ratio determined by GLC (Cyclodex-β column or DB-1701 column using MTPA ester) or HPLC (Chiralcel OD-H column). [d] Isolated yields.

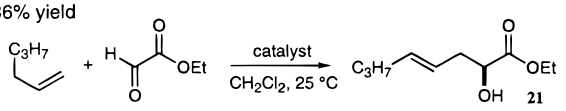
Ene reactions with trisubstituted cyclic olefins were also investigated using [Cu((*S*,*S*)-*t*-Bu-box)$(H_2O)_2$]$(SbF_6)_2$ (**4**) and [Cu((*S*,*S*)-Ph-box)]$(OTf)_2$ (**1c**) (eq 9). The addition of 1-methylcyclohexene to ethyl glyoxylate was catalyzed by **4** to produce (*S*)-**20** in excellent enantioselectivity and modest diastereoselectivity uncontaminated with regiochemical isomers (86%, 98% ee, endo:exo 78:22). Complex **1c** afforded (*R*)-**20** in good enantioselectivity and higher diastereoselectivity, again without any regiochemical products isolated (86%, 92% ee, endo:exo



(9)

[Cu(*t*-Bu-box)$(H_2O)_2$]$(SbF_6)_2$ (**4**) (1 mol%): 98% ee (*S*), *endo:exo* 78:22, 86% yield

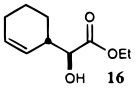
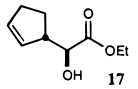
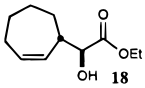
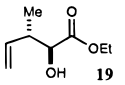
[Cu(Ph-box)]$(OTf)_2$ (**1c**) (10 mol%): 92% ee (*R*), *endo:exo* 89:11, 86% yield



(10)

[Cu((*S*,*S*)-*t*-Bu-box)]$(SbF_6)_2$ (**2a**) (10 mol%): 92% ee (*S*), *E:Z* 96:4, 96% yield

Table 6. Catalyzed Enantioselective Ene Reactions between Ethyl Glyoxylate and 1,2-Disubstituted Olefins[a]

olefin	product[b]	cat (mol%)	% ee[c]	% yield[d]	ratio[c]
	 **16**				*endo:exo*
		2a (10)	98 (*S*)	95	86:14
		1c (10)	94 (*R*)	70	95:5
	 **17**				*endo:exo*
		2a (10)	96 (*S*)	83	66:33
		2c (10)	78 (*R*)	72	73:27
	 **18**				*endo:exo*
		2a (10)	nd	<30	nd
		2c (10)	nd	<30	nd
Me Me	 **19**				*anti:syn*
		2a (10)	98 (*S*)	54	40:60
		2c (10)	90 (*R*)	60	88:12

[a] All reactions performed at 0.33 M in substrate in CH_2Cl_2 at 25 °C. [b] Absolute configurations assigned by X-ray crystal analysis or by analogy (Supporting Information). [c] Enantiomeric excess and diastereoselectivity determined by GLC (Cyclodex-β column). [d] Isolated yields. nd = not determined.

89:11). The absolute and relative stereochemistry of **20** was determined by X-ray crystallography of the derived α-methylbenzylamide. Unfortunately, the analogy provided by methylcyclohexene (eq 9) does not extend to either 1-methylcyclopentene or 1-methylcycloheptene which afford multiple regiochemical isomers.

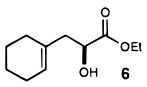
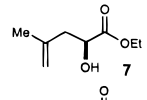
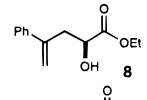
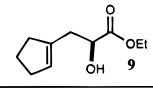
To date, no catalytic enantioselective ene reactions with significantly less nucleophilic monosubstituted olefins have been reported.[19] However, with complex [Cu((*S*,*S*)-*t*-Bu-box)$(SbF_6)_2$ (**2a**), 1-hexene is a viable substrate in this reaction affording ethyl (*S*)-2-hydroxy-4-octenoate (**21**) in 98% ee with excellent (*E*) olefin selectivity (96:4) (eq 10). The absolute configuration of the ene product **10** was determined by sequential hydrogenation and reduction to afford (2*S*)-octane-1,2-diol for which the spectral data and optical rotation were identical to that reported in the literature.[20]

To demonstrate the preparative utility of this methodology, the reaction of ethyl glyoxylate with methylene cyclohexane was conducted on a 25-mmol scale employing 0.2 mol % (43 mg) of the Cu(II)-box catalyst **4** to generate the desired adduct **6** (4.3 g) in high yield and enantioselectivity (86%, 97% ee).

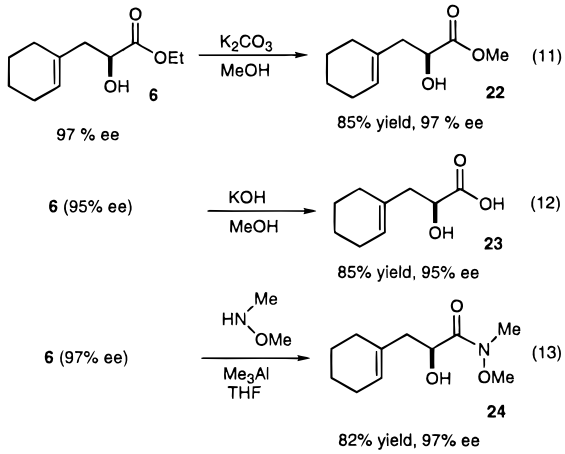
One potential limitation of the glyoxylate−ene reaction is the need to use freshly distilled ethyl glyoxylate. It was found that with an increased reaction time (24 h) comparable yields and enantioselectivities could be realized using polymeric ethyl glyoxylate solutions directly (Table 7).[21] While small amounts of monomeric glyoxylate are present in undistilled glyoxylate, it appears that catalysts **4** and **1c** are able to catalyze the depolymerization of the glyoxylate. In an experiment using undistilled glyoxylate with 3 equiv of methylene cyclopentane, catalyst **4** afforded (*S*)-**9** in 98% yield and 97% ee.

Derivatization Reactions. The α-hydroxy ester ene products are versatile chiral building blocks. Commercially availabl ethyl glyoxylate is the logical choice for use in these reactions; however, if other esters are desired, simple base-promoted transesterification is possible. For example, treatment of **6** with K_2CO_3 in MeOH affords **22** in 85% yield without detectable racemization (eq 11). Racemization-free ester hydrolysis is also possible. Treatment of ester **6** with aqueous KOH in MeOH affords acid **23** in 85% yield (eq 12). Weinreb amides are useful intermediates for many organic transformations.[22] Treatment of **6** with *N*,*O*-dimethylhydroxylamine hydrochloride and trimethylaluminum in THF at reflux afforded the amide **24** in 82% yield (eq 13). NMR spectroscopic analysis of the Mosher esters derived from adducts **22**−**24** indicated no racemization had occurred in any of these reactions.

Table 7. Catalyzed Enantioselective Ene Reactions Using Distilled and Undistilled Ethyl Glyoxylate with 1,1-Disubstituted Olefins[a]

			distilled glyoxylate		undistilled glyoxylate[b]	
olefin	product	cat (mol%)	% ee[c]	% yield[d]	% ee[c]	% yield[d]
	 **6**	**4** (1)	97 (*S*)	90	98 (*S*)	92
		1c (10)	87 (*R*)	99	84 (*R*)	80
Me Me	 **7**	**4** (1)	96 (*S*)	83	96 (*S*)	98
		1c (10)	92 (*R*)	92	94 (*R*)	73
Ph Me	 **8**	**4** (1)	93 (*S*)	97	94 (*S*)	99
		1c (10)	89 (*R*)	99	90 (*R*)	92
	 **9**	**4** (1)	96 (*S*)	95	97 (*S*)	85
		1c (10)	76 (*R*)	97	80 (*R*)	96

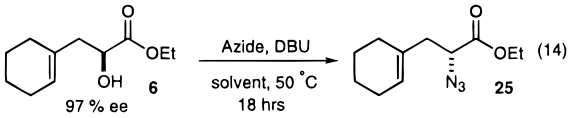
[a] All reactions performed at 0.33 M in substrate in CH_2Cl_2 at 0 °C. [b] Fluka Brand 50% glyoxylate in toluene solution. [c] Enantiomeric excess determined by GLC (Cyclodex-b column). [d] Isolated yields.



Azide displacement of the alcohol **6** provides a facile entry into the synthesis of orthogonally protected unusual α-amino acids.[23] Initial attempts at azide displacement using diphenyl phosphorazidate (DPPA) in refluxing toluene[24] afforded the α-azido ester **25** in 63% yield; however, the product was racemic (Table 8, entry 1). Use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the limiting reagent (0.95 equiv) resulted in extensive racemization (entry 2: 20% ee). Fortunately, the more reactive bis(*p*-nitrophenyl) phosphorazidate ($(NO_2)_2$DPPA)[25] reagent afforded the desired product in higher enantioselectivities, with DMF being the optimal solvent (entries 3−8). The use of 1.2 equiv of DBU resulted in product with 80% ee (entry 6), while

(19) For chiral auxiliary examples see: Whitesell, J. K.; Lawrence, R. M.; Chen, H.-H. *J. Org. Chem.* **1986**, *51*, 4779−4784.
(20) Otera, J.; Niibo, Y.; Nozaki, H. *Tetrahedron* **1991**, *47*, 7625−7634.
(21) Fluka 50% glyoxylate in toluene solution.
(22) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. For a review see: Sibi, M. P. *Org. Prep. Proc. Int.* **1993**, *25*, 15−40.
(23) For a review on the use of azides see: Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297−368.
(24) Thompson, A. S.; Humphrey, G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886−5888.
(25) Mizuno, M.; Shioiri, T. *J. Chem Soc., Chem. Commun.* **1997**, 2165−2166. For the synthesis of $(NO_2)_2$DPPA see: Shioiri, T.; Yamada, S.-I. *Chem. Pharm. Bull.* **1974**, *22*, 855−858.

Table 8. Azide Displacement Conditions for Alcohol **6** (Eq 14)



entry	Azide	Solvent	Equiv DBU	% ee [a]	% yield [b]
1[c]	DPPA	PhMe	1.2	0	63
2[c]	DPPA	PhMe	0.95	20	61
3	$(NO_2)_2$ DPPA	PhMe	1.2	83	86
4	$(NO_2)_2$ DPPA	PhMe	0.95	87	nd
5	$(NO_2)_2$ DPPA	THF	0.95	93	60
6	$(NO_2)_2$ DPPA	DMF	1.2	80	81
7	$(NO_2)_2$ DPPA	DMF	0.95	≥95	72
8[d]	$(NO_2)_2$ DPPA	DMF	0.95	≥95	75

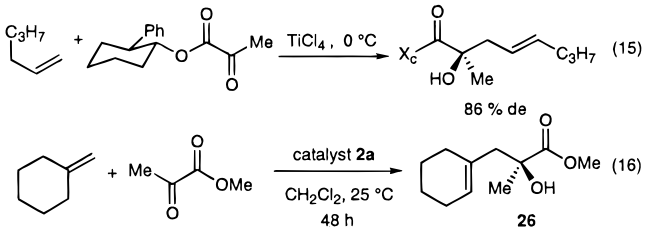
[a] Enantiomeric excess determined by GLC (Cyclodex-β column). [b] Isolated yields. [c] Reflux. [d] Reaction time 36 h. nd = not determined.

the use of 0.95 equiv of DBU resulted in product with ≤2% racemization and in good yield (entries 6 and 7: 72−75% yield).

Ene Reaction of Pyruvate Esters

The carbonyl−ene reaction with ketones has not been well studied, although it provides a simple route to homoallylic tertiary alcohols. To date, no enantioselective catalytic variants of this process have been reported. In a relevant study, Whitesell has reported the reaction of the pyruvate ester of *trans*-2-phenylcyclohexanol with 1-hexene in the presence of 2 equiv of $TiCl_4$ (eq 15).[26]

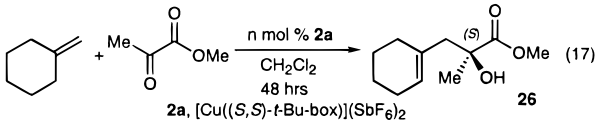
In initial experiments, [Cu((*S*,*S*)-*t*-Bu-box)]$(SbF_6)_2$ complex (**2a**) was found to promote the addition of methylenecyclohexane to methyl pyruvate in excellent enantioselectivity (>99% ee), but in low yields (35%) (eq 16). Other Cu(II)-box catalysts were found to afford lower enantioselectivities.



[Cu((*S*,*S*)-*t*-Bu-box)]$(SbF_6)_2$ (**2a**) (10 mol%): >99 %ee, 35% yield

Reaction Optimization. Optimization of the reaction between methylenecyclohexane and methyl pyruvate catalyzed by [Cu((*S*,*S*)-*t*-Bu-box)]$(SbF_6)_2$ (**2a**) is shown in Table 9. When the olefin was used as the limiting reagent, the yield did not improve and isolation of the ene product from pyruvate decomposition products was difficult (entry 1). A reaction employing 50 mol % catalyst **2a** was followed by in situ infrared spectroscopy. Rapid consumption of starting material was observed; however, no free alcohol appeared during this time. Product isolation after 12 h resulted in a 50% yield of **25** with >99% ee (entry 3). The reaction appears to be facile; however, catalyst turnover appears slow. Although the use of THF as solvent has been shown to facilitate catalyst turnover,[27] no reaction was observed in this case (entry 4). When the reaction was warmed to reflux,

Table 9. Optimization of the Catalyzed Ene Reaction between Methylene Cyclohexane and Methyl Pyruvate (Eq 17)

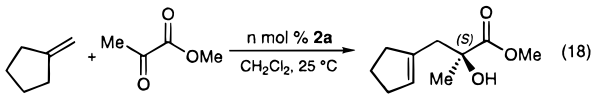


2a, [Cu((*S*,*S*)-*t*-Bu-box)]$(SbF_6)_2$

entry	equiv olefin	equiv pyruvate	cat (mol%)	T, °C	% ee [a]	% yield [b]
1	1.0	5.0	10	25	98	30 [c]
2	5.0	1.0	10	25	99	35
3	5.0	1.0	50	25	>99	50
4[d]	5.0	1.0	10	25	nd	nr [e]
5	5.0	1.0	10	40	98	50
6	10.0	1.0	10	40	98	71
7	10.0	1.0	20	40	98	84

[a] Enantiomeric excess determined by GLC (Cyclodex-β column). [b] Isolated yields. [c] Large amounts of pyruvate decomposition products. [d] THF as solvent. [e] No reaction. nd = not determined.

Table 10. Optimization of the Catalyzed Ene Reaction between Methylene Cyclopentane and Methyl Pyruvate (Eq 18)



2a, [Cu((S,S)-t-Bu-box)]$(SbF_6)_2$

entry	olefin (equiv)	cat (mol%)	time (h)	% ee [a, b]	% yield [c]
1	5.0	5	48	98	63
2	5.0	10	24	>99	74
3	5.0	10	48	>99	90
4	10.0	10	48	>99	95
5[d]	5.0	5	48	98	98

[a] Enantiomeric excess determined by GLC (Cyclodex-b column). [b] Absolute configuration assigned by X-ray crystal analysis (Supporting Information). [c] Isolated yields. [d] 40 °C.

catalyst turnover was improved with little loss in enantioselectivity (entries 5 and 6: 98% ee). Use of 10 equiv of olefin and 20 mol % catalyst afforded an 84% yield (entry 6).

As shown in Table 10, the reaction of methylenecyclopentane with methyl pyruvate was more facile, requiring 10 mol % catalyst and 25 °C to obtain **27** in excellent enantioselectivity and yield (entry 4: 90%, >99% ee). Lower catalyst loadings could be used when the reaction was heated to reflux (entry 5: 98%, 98% ee).

Reaction Scope. The scope of the pyruvate−ene reaction was further investigated using other 1,1-disubstituted olefins (Table 11). Optimal results were obtained with 10 mol % [Cu(*S*,*S*)-*tert*-butyl-bis(oxazolinyl)]$(SbF_6)_2$ (**2a**) in the reaction of methyl pyruvate with an excess of isobutylene (**28**: 76%, 98% ee).[28] α-Methylstyrene (10 equiv) also reacted smoothly in the presence of 5 mol % **2a**, to afford ene adduct **29** in 88% yield and in 98% ee. The absolute configuration of **27** was determined by hydrolysis to the free acid, followed by X-ray crystallographic analysis of the 1-(1-naphthyl)ethylammonium salt (Supporting Information). The absolute configurations of compounds **26**, **28**, and **29** are based on analogy. Further development of the pyruvate−ene reaction is currently underway.

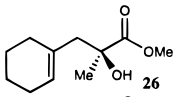
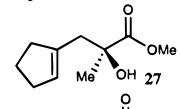
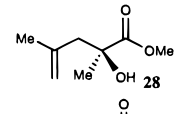
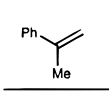
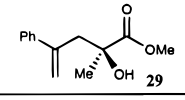
Reaction Stereochemistry. The preceding study demonstrates that *t*-Bu-box Cu(II) catalysts exhibit stereoregular behavior in reactions involving a broad range of substrates capable of chelation. X-ray crystallography, double stereodifferentiating reactions, PM3 semiempirical calculations, and EPR spectroscopy all support bidentate coordination of the substrate

(26) Whitesell, J. K.; Deyo, D.; Bhattacharya, A. *J. Chem. Soc., Chem. Commun.* **1983**, 802. For a correction see: Whitesell, J. K.; Nabona, K.; Deyo, D. *J. Org. Chem.* **1989**, *54*, 2258. Reaction between *N*-glyoxyloyl-(2*R*)-borane-10,2-sultam and monosubstituted olefins has also been reported: Jezewski, A.; Chajewska, K.; Wielogórski, Z.; Jurczak, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1741−1749.

(27) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686−699.

(28) Due to the volatility of isobutylene, the reactions were performed in sealed tubes (see Supporting Information).

Table 11. Catalyzed Enantioselective Ene Reactions between Methyl Pyruvate and 1,1-Disubstituted Olefins[a]

olefin	product[b]	cat (mol%)	% ee[c]	% yield[d]
	 **26**	**2a** (20)	98 (*S*)	84
	 **27**	**2a** (5)	98 (*S*)	95
	 **28**	**2a** (10)	98 (*S*)	76
	 **29**	**2a** (5)	98 (*S*)	94

[a] All reactions performed at 0.33 M in substrate in CH_2Cl_2 at 40 °C. [b] Absolute configurations assigned by X-ray crystal analysis or by analogy (Supporting Information). [c] Enantiomeric excess determined by GLC (Cyclodex-β column). [d] Isolated yields.

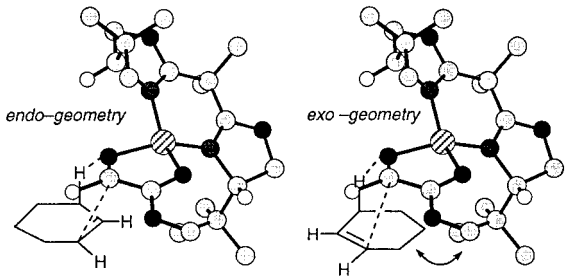
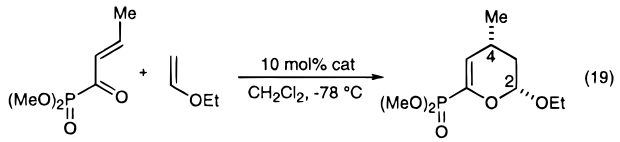


Figure 2. Endo/exo approach of cyclohexene to the [Cu((*S*,*S*)-*t*-Bu-box)(glyoxylate)]$^{2+}$.

to a distorted square planer Cu(II) ligand complex.[29] Consistent with these results, the Re face of the coordinated glyoxylate (or pyruvate) is encumbered by the *t*-Bu group on the ligand resulting in the generation of the (*S*)-configured alcohol (Figure 2).

In the ene reaction, it has been suggested that endo/exo selectivity is largely by steric interactions rather than electronic effects.[30] In the reaction between cyclohexene and ethyl glyoxylate catalyzed by [Cu(*S*,*S*)-*t*-Bu-box)]$(SbF_6)_2$ (**2a**) and [Cu((*S*,*S*)-Ph-box)]$(OTf)_2$ (**1c**), the endo approach of the olefin is preferred (**2a**, endo:exo 86:14; **1c**, endo:exo 95:5). As illustrated in Figure 2, it seems reasonable to speculate that exo approach of the olefin is disfavored due to the developing steric interaction between the *t*-Bu group on the ligand and the cyclohexene.

The rationale for the turnover in selectivity in the glyoxylate-ene reaction catalyzed by [Cu((*S*,*S*)-Ph-box)]X_2 complexes **1c** and **2c** is not fully understood at this time. This turnover in selectivity has also been observed in our work in the inverse demand hetero-Diels−Alder reaction (eq 19).[7h] A change in metal geometry from square planar to tetrahedral has been proposed to account for this reversal in enantioselectivity;[31] however, we have argued elsewhere that a change in geometry at the metal center is not necessarily responsible for this altered stereochemical outcome.[32]



1a: [Cu((*S*,*S*)-*t*-Bu-box)](OTf)$_2$: 99% ee (*2R, 4R*), *endo:exo* 99:1
1c: [Cu((*S*,*S*)-Ph-box)](OTf)$_2$: 94% ee (*2S, 4S*), *endo:exo* >99:1

Conclusions

This study documents the use of C_2-symmetric Cu(II) complexes **1**, **2**, and **4** to enantioselectively catalyze the carbonyl−ene reaction. The principal attribute of these complexes is their high level of Lewis acidity that affords an expanded scope for the glyoxylate−ene process that extends to all olefin-substitution patterns. The practical utility of the methodology has been demonstrated by the use of low catalyst loading (0.2−10 mol %), moderate temperatures (0−25 °C), and commercially available undistilled glyoxylate. This methodology has been shown to be preparatively useful by the execution of a glyoxylate−ene reaction on a 25-mmol scale using only 0.2 mol % of the bench stable catalyst **4**. Additionally, the first example of an enantioselective catalytic reaction of pyruvate esters with 1,1-disubstituted olefins has been accomplished using catalyst **2a** in high enantioselectivities and yields.

Experimental Section[33]

(*S*,*S*)-Bis(*tert*-butyloxazoline) and (*S*,*S*)-bis(phenyloxazoline) and the corresponding Cu(II) complexes **1**, **2**, and **4** were prepared as previously described.[34] These ligands are also commercially available from Aldrich Chemical Co. Ethyl glyoxylate was purchased from Fluka as a 50% solution in toluene and used as detailed below.

Distillation Procedure for Ethyl Glyoxylate. To an oven-dried, 25-mL round-bottom flask fitted with a magnetic stirring bar and a short path distillation apparatus was added 10 mL of ethyl glyoxylate/toluene solution. The distillation pot was warmed to 140−150 °C to remove most of the toluene (head temperature 110−118 °C). The distillation pot was then warmed to 160−170 °C and the remaining ethyl glyoxylate/toluene was collected (head temperature 120−130 °C). ^{1}H NMR spectroscopic analysis indicates the distilled glyoxylate solution to be typically a 8:2 mixture of ethyl glyoxylate:toluene.

Method A: General Procedure for the Addition of Olefins to Ethyl Glyoxylate Catalyzed by 1 and 2. To an oven-dried, 10-mL round-bottom flask containing a magnetic stirring bar was added the olefin (0.50 mmol) and ethyl glyoxylate (3−10 equiv). To this mixture was added the catalyst solution **1** or **2** (0.05−0.005 mmol in 1.5 mL of CH_2Cl_2) in one portion. After the reaction was complete (1−48 h) the mixture was directly loaded onto a 2 × 6 cm silica gel flash column and eluted with the indicated solvent to provide the title compounds.

Method B: General Procedure for the Addition of Olefins to Ethyl Glyoxylate Catalyzed by 4. To an oven-dried, 10-mL round-bottom flask containing a magnetic stirring bar was added the olefin (0.50 mmol), ethyl glyoxylate (3−10 equiv), and CH_2Cl_2 (1.5 mL). To this solution was added solid **4** (0.05−0.005 mmol) in one portion.

(29) X-ray crystallography: (a) Reference 13. (b) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. T. *J. Am. Chem. Soc.* **1999**, *121*, 1994. Double stereodifferentiating experiments: (c) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460. PM3 and EPR experiments: (d) Reference 8b,d.

(30) Snider, B. In *Comprehensive Organic Synthesis;* Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol 2, pp 527−561.

(31) (a) Johannsen, M.; Jørgensen, K. A. *J. Org. Chem.* **1995**, *60*, 5757. (b) Johannsen, M.; Yao, S.; Jørgensen, K. A. *Chem. Commun.* **1997**, 2169. (c) Johannsen, M.; Yao, S.; Graven, A.; Jørgensen, K. A. *Pure Appl. Chem.* **1998**, *70*, 1117.

(32) (a) Evans, D. A.; Johnson, J. S.; Burgey, C. S.; Campos, K. R. *Tetrahedron Lett.* **1999**, *40*, 2879−2882. (b) Reference 7h.

(33) General Information is provided in the Supporting Information. The following are also contained in the Supporting Information: specific reaction conditions, characterization data, and absolute and relative stereochemical proofs.

(34) (a) For the preparation of (*S*,*S*)-bis(*tert*-butyloxazoline) see: ref 14. (b) For the preparation of (*S*,*S*)-bis(phenyloxazoline) see: Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728−9. For the preparation of the Cu(II) complexes see: (c) ref 27 and (d) ref 14.

After the reaction was complete (1−48 h) the mixture was directly loaded onto a 2 × 6 cm silica gel flash column and eluted with the indicated solvent to provide the title compounds.

Acknowledgment. Support for this research was provided by the NSF (CHE-9633581) and the NIH (GM-33328). The NIH BRS Shared Instrumentation Grant Program 1-S10-RR04870 and the NSF (CHE 88-14019) are acknowledged for providing NMR facilities. The amino alcohols and acids utilized in the preparation of the box ligands were generously provided by NSC Technologies.

Supporting Information Available: Complete experimental procedures and characterization of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA000913T