ORGANIC LETTERS

2003
Vol. 5, No. 20
3749−3752

Chiral Lewis Acid-Catalyzed Enantioselective Intramolecular Carbonyl Ene Reactions of Unsaturated α-Keto Esters

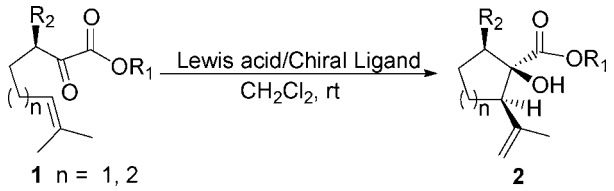
Dan Yang,* Min Yang, and Nian-Yong Zhu

Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong, P. R. China

yangdan@hku.hk

Received August 6, 2003

ABSTRACT



1 n = 1, 2 **2**

Chiral Lewis acid-promoted highly enantioselective intramolecular carbonyl ene reactions of unsaturated α-keto esters have been investigated. In the presence of chiral Lewis acids such as [Sc((*R*,*R*)-Ph-pybox)](OTf)$_3$ and [Cu((*S*,*S*)-Ph-box)](OTf)$_2$, several unsaturated α-keto esters underwent carbonyl ene reactions in CH_2Cl_2 at room temperature to give monocyclic products in good yield and excellent enantioselectivity.

The carbonyl ene reaction attracts much attention because of its convenience for the construction of carbon−carbon bonds. In recent years, significant progress has been made in enantioselective intermolecular carbonyl-ene reactions catalyzed by chiral Lewis acids.[1] However, there are few examples of enantioselective intramolecular carbonyl ene reactions of unsaturated aldehydes,[2] despite the wide applications of intramolecular carbonyl ene reactions in the total synthesis of natural products.

Recently, we reported Lewis acid-catalyzed bromo atom transfer radical cyclization of α-bromo β-keto esters and phenylseleno group transfer tandem radical cyclization of α-phenylseleno β-keto amides.[3] In an effort to extend those reactions to α-keto esters, Lewis acid $Mg(ClO_4)_2$ was used to promote the radical cyclization of α-keto ester **1a** with Et_3B/O_2 as the radical initiator. Interestingly, we found that, instead of the radical cyclization product **5**, product **2a** of an intramolecular carbonyl ene reaction was obtained in 51% yield (eq 1). Similarly, in the presence of Lewis acid $MgBr_2$, the opening of epoxide **6** did not stop at **1b** but instead gave carbonyl ene reaction product **2b** in 44% yield (eq 2). These

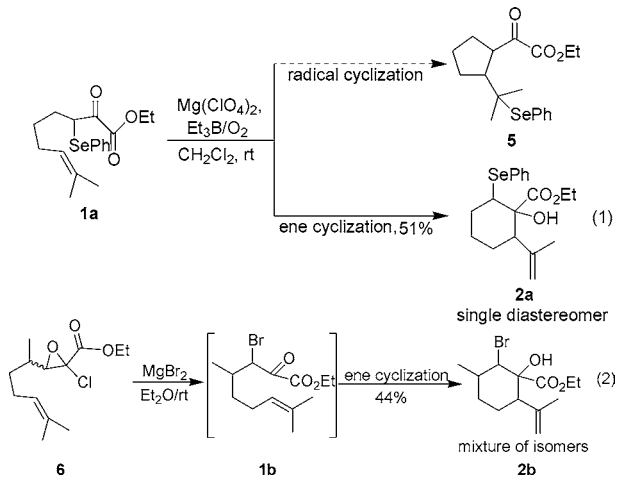
(1) (a) For a recent review, see: Mikami, K.; Terada, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Wiley: New York, 2000; Vol. 3, Chapter 32, pp 1140−1174. (b) Mikami, K. *Pure Appl. Chem.* **1996**, *68*, 639−644. For recent examples, see: (c) Mauruoka, K.; Hoshino, Y.; Shirasaka, T.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 3967−3970. (d) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949−3954. (e) Qian, C.; Huang, T. *Tetrahedron Lett.* **1997**, *38*, 6721−6724. (f) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824−5825. (g) Gao, Y.; Lane-Bell, P.; Vederas, J. C. *J. Org. Chem.* **1998**, *63*, 2133−2143. (h) Gethergood, N.; Jørgensen, K. A. *Chem. Commun.* **1999**, 1869−1870. (i) Reichel, F.; Fang, X.; Yao, S.; Ricci, M.; Jørgensen, K. A. *Chem. Commun.* **1999**, 1505−1506. (j) Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936−7943. (k) Hao, J.; Hatano, M.; Mikami, K. *Org. Lett.* **2000**, *2*, 4059−4062. (l) Koh, J. H.; Larsen, A. O.; Gagne, M. R. *Org. Lett.* **2001**, *3*, 1233−1236. (m) Kezuka, S.; Ikeno, T.; Yamada, T. *Org. Lett.* **2001**, *3*, 1937−1939. (n) Becker, J. J.; van Orden, L. J.; White, P. S.; Gagne, M. R. *Org. Lett.* **2002**, *4*, 727−730.

(2) (a) Sakane, S.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1985**, *26*, 5535−5538. (b) Ziegler, F. E.; Sobolov, S. B. *J. Am. Chem. Soc.* **1990**, *112*, 2749−2758. (c) Mikami, K.; Sawa, E.; Terada, M. *Tetrahedron: Asymmetry* **1991**, *2*, 1403−1412. (d) Mikami, K.; Terada, M.; Sawa, E.; Nakai, T. *Tetrahedron Lett.* **1991**, *32*, 6571−6574.

(3) (a) Yang, D.; Gu, S.; Yan, Y.-L.; Zhu, N.-Y.; Cheung, K.-K. *J. Am. Chem. Soc.* **2001**, *123*, 8612−8613. (b) Yang, D.; Gu, S.; Yan, Y.-L.; Zhao, H.-W.; Zhu, N.-Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 3014−3017. (c) Yang, D.; Gao, Q.; Lee, O.-L. *Org. Lett.* **2002**, *4*, 1239−1241.

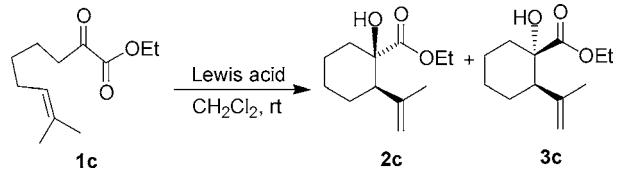
10.1021/ol035486d CCC: $25.00
Published on Web 09/12/2003

observations led us to investigate the Lewis acid-promoted ene cyclization of α-keto esters, since in the absence of Lewis acids, intramolecular carbonyl ene reactions of α-keto esters proceeded at high temperatures for several days as reported by Hiersemann.[4] Here we report highly enantioselective intramolecular carbonyl ene reactions of unsaturated α-keto esters catalyzed by chiral Lewis acids.[5]



Our work began with the transformation of **1c** into **2c** with a series of Lewis acid catalysts (Table 1). No cyclization took place in the absence of Lewis acid (entry 1), whereas the addition of 1 equiv of Lewis acid significantly accelerated the reactions (2−6). $Mg(ClO_4)_2$ and $Yb(OTf)_3$ gave notably higher yields of cyclization products (69 and 84%, respectively) than $Cu(OTf)_2$ and $Zn(OTf)_2$ in CH_2Cl_2 (entries 2−5). $Sc(OTf)_3$ also gave ene cyclization product in moderate yield (56%, entry 6). These Lewis acid-promoted ene cyclization reactions exhibited excellent stereoselectivity for the major product **2c**, in which the 1-hydroxy group was cis to the 2-allyl group.

Table 1. Lewis Acid-Promoted Carbonyl Ene Reactions of **1c**[a]

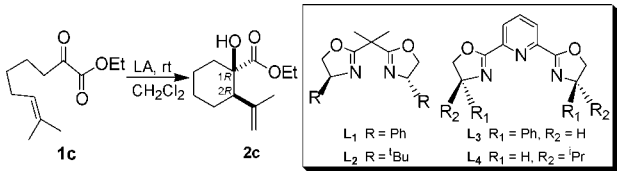


entry	Lewis acid (1.0 equiv)	time (h)	conversion (%)[b]	yield (%) (**2c**:**3c**)[c]
1		18	0	0
2	$Mg(ClO_4)_2$	4	92	69 (33:1)
3	$Yb(OTf)_3$	6	90	84 (20:1)
4	$Cu(OTf)_2$	5	91	43 (23:1)
5	$Zn(OTf)_2$	36	60	23 (26:1)
6	$Sc(OTf)_3$	5	94	56 (30:1)

[a] Unless otherwise indicated, all reactions were carried out at room temperature with 0.1−0.2 mmol of substrate (0.05 M in CH_2Cl_2). [b] Determined by ^{1}H NMR with α-methyl stilbene as the internal standard. [c] Ratio of **2c** and **3c** was determined by ^{1}H NMR analysis of crude products. Compounds **2c** and **3c** were separable by flash column chromatography. Stereochemistry of **2c** was determined by the analysis of its NOESY spectra.

We then investigated enantioselective carbonyl ene reactions by adding chiral ligands[6] to the reaction system (Table 2). In the presence of chiral ligand (*S*,*S*)-*t*-Bu-box (**L**$_2$), neither $Mg(ClO_4)_2$ nor $Cu(OTf)_2$ could catalyze this ene reaction (entries 1 and 6). Similarly, the combination of $Yb(OTf)_3$ and chiral ligand (*R*,*R*)-Ph-pybox (**L**$_3$) or (*S*,*S*)-*i*-Pr-pybox (**L**$_4$) proved to be ineffective (entries 2 and 3). In contrast, entries 4, 5, and 7 showed ligand-accelerated catalysis,[7] that is, chiral Lewis acid complexes [Sc((*R*,*R*)-Ph-pybox)]$(OTf)_3$, [Zn((*S*,*S*)-Ph-box)]$(OTf)_2$, and [Cu((*S*,*S*)-Ph-box)]$(OTf)_2$ not only increased the yields of **2c** (up to

Table 2. Chiral Lewis Acid-Promoted Carbonyl Ene Reactions of **1c**[a]



entry	Lewis acid (equiv)	ligand (equiv)[b]	time (h)	conversion (%)[c,d]	yield (%)[c,d]	ee (%)[e,f]
1	$Mg(ClO_4)_2$ (1.0)	L_2 (1.1)	48	76 (92)	0 (69)	
2	$Yb(OTf)_3$ (0.2)	L_3 (0.22)	44	33 (90)	0 (84)	
3	$Yb(OTf)_3$ (0.2)	L_4 (0.22)	44	30	0	
4	$Sc(OTf)_3$ (0.2)	L_3 (0.22)	6	91 (94)	86 (56)	88[g]
5	$Zn(OTf)_2$ (1.0)	L_1 (1.1)	48	73 (60)	54 (23)	54
6	$Cu(OTf)_2$ (1.0)	L_2 (1.1)	14	0 (91)	0 (43)	
7	$Cu(OTf)_2$ (1.0)	L_1 (1.1)	6	96	90	87[g]
8[h]	$Cu(OTf)_2$ (1.0)	L_1 (1.1)	2	96	89	90[g]
9	$Cu(OTf)_2$ (0.2)	L_1 (0.22)	3	91	81	91[g]
10[i]	$Cu(OTf)_2$ (0.2)	L_1 (0.22)	24	41	32	
11[j]	$Cu(OTf)_2$ (0.2)	L_1 (0.22)	32	38	0	
12	$Cu(SbF_6)_2$ (1.0)	L_1 (1.1)	30	23	8	
13	$Cu(H_2O)_2(SbF_6)_2$ (1.0)	L_2 (1.1)	41	58	28	

[a] Unless otherwise indicated, all reactions were carried out at room temperature with 0.1−0.2 mmol of substrate (0.1 M in CH_2Cl_2). [b] Ligand **L**$_3$ has an (*R*,*R*)- configuration, while the other ligands have an (*S*,*S*)-configuration. [c] Determined by ^{1}H NMR with α-methyl stilbene as the internal standard. [d] Numbers in parentheses represent the value in the absence of chiral ligand. [e] Enantiomeric excess was determined by HPLC analysis using a Chiral AD column. [f] Absolute configuration of the major enantiomer was determined to be (1*R*,2*R*)- by X-ray crystallographic analysis of its *p*-bromobenzene sulfonate derivative. [g] Diastereomeric ratio was greater than 50:1 as determined by ^{1}H NMR analysis of the crude product. [h] Activated 4 Å molecular sieves (powder, 500 mg/mmol substrate) were added to the reaction mixture. [i] Et_2O as the solvent. [j] THF as the solvent.

(4) (a) Hiersemann, M. *Synlett* **2000**, 415−417. (b) Hiersemann, M. *Eur. J. Org. Chem.* **2001**, 483−491.

(5) While our work was ongoing, Hiersemann and co-workers reported a chiral Lewis acid-catalyzed asymmetric domino Claisen rearrangement/intramolecular carbonyl ene reaction with excellent enantioselectivity. However, only one substrate was investigated and the detail of the intramolecular carbonyl ene reaction was not examined. Kaden, S.; Hiersemann, M. *Synlett* **2002**, 1999−2002.

(6) For reviews on C_2-symmetric chiral bis(oxazoline)-Lewis acid complexes as catalysts, see: (a) Pfaltz, A. *Acta Chem. Scand.* **1996**, *50*, 189−194. (b) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1−45. (c) Jørgensen, K. A.; Johannsen, M.; Yao, S.; Audrain, H.; Thorhauge, J. *Acc. Chem. Res.* **1999**, *32*, 605−613. (d) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335.

(7) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059−1070.

90% yield, entry 7) but also exhibited good to excellent stereocontrol. For entries 4 and 9, the enantioselectivity was reversed because the absolute configurations of the chiral ligands were opposite. The addition of activated 4 Å molecular sieves did not have an obvious effect on the reaction (entry 8). The loading of Lewis acid could be reduced to as low as 20 mol % with no loss in ee (entries 7 vs 9), and up to 91% ee was obtained for the ene cyclization of **1c**. When [Cu((*S*,*S*)-Ph-box)](OTf)$_2$ and Sc[(*R*,*R*)-Ph-pybox)](OTf)$_3$ were used as the catalyst, the diastereomeric ratio was greater than 50:1 (entries 4 and 7−9).

These ene cyclizations were found to be solvent dependent. For catalyst [Cu((*S*,*S*)-Ph-box)](OTf)$_2$, CH_2Cl_2 was a better solvent than Et_2O (entries 9 vs 10), whereas compound **2c** was not obtained in THF (entry 11). The counterions[8] also affected the catalyst efficiency of the Cu(II) Lewis acids. When the counterion was changed from OTf^- to noncoordinating SbF_6^-, the yield of **2c** decreased dramatically (entries 8 vs 12). Compared to Cu[(*S*,*S*)-*t*-Bu-box](OTf)$_2$, the use of catalyst Cu[(*S*,*S*)-*t*-Bu-box)$(H_2O)_2$] $(SbF_6)_2$[9] did not give much improvement to the yield of **2c** (entries 6 vs 13). Therefore, in CH_2Cl_2 at room temperature, the catalysts [Cu((*S*,*S*)-Ph-box)](OTf)$_2$[10] and Sc[(*R*,*R*)-Ph-pybox)](OTf)$_3$[11] were found to be efficient for the intramolecular carbonyl ene reactions of **1c**.

The observed stereoselectivity may be explained by invoking the transition state models proposed by Jørgensen et al. for the intermolecular carbonyl ene reactions (Figure 1).[12] The [Cu((*S*,*S*)-Ph-box)](OTf)$_2$ complex is assumed to

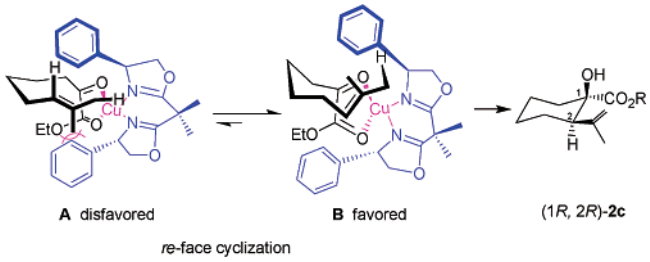
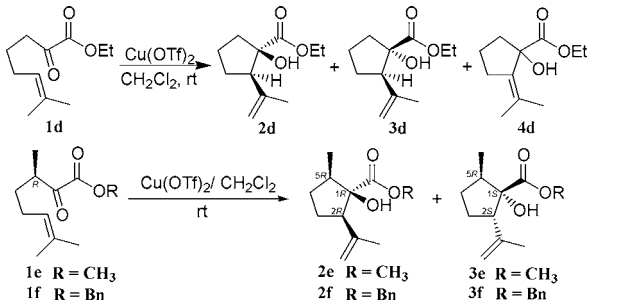


Figure 1. Proposed transition-state model for the {Cu[(*S*,*S*)-Ph-box]} complex-promoted carbonyl ene cyclization reaction of **1c**.

chelate with the dicarbonyl moiety of the substrate in a tetrahedral-like geometry.[12a,c] Considering the steric interactions between substituents on the olefinic C=C double bond and the phenyl groups of the chiral ligand (*S*,*S*)-Ph-box, the ene cyclization from the *re*-face (transition states **A** and **B**) should be more favorable than that from the *si*-face (not shown). In addition, because of the lack of steric interactions between methyl substituent on the olefinic C=C double bond and the phenyl group, transition state **B** would be favored over **A**, resulting in the cyclization product of (1*R*,2*R*)-configuration and a cis relationship between the 1-hydroxyl group and the 2-alkyl group.

Several other substrates **1d**−**f** were tested under the aforementioned carbonyl ene cyclization conditions (Table 3). In the presence of 0.2 equiv of Lewis acid Cu(OTf)$_2$ without ligand, the ene cyclization of **1d** gave cyclopentane products **2d** and **3d** in poor yield (55%), together with a double bond-rearranged product **4d** (entry 1). However, 0.5 equiv of chiral Lewis acid [Cu((*S*,*S*)-Ph-box)](OTf)$_2$ catalyzed the cyclization of **1d** in good yield and ee (87 and 75%, respectively; entry 2). Reducing the loading of the chiral Lewis acid led to a slightly decreased yield (78%) and ee (71%) (entries 2 vs 3). Furthermore, the addition of chiral ligands gave improved diastereoselectivity (entries 1−3).

Table 3. Asymmetric Carbonyl Ene Reaction of **1d**−**f**[a]



entry	substrate	time (h)	ligand (equiv)	yield of **2** (%)[b]	dr (**2**:**3**)[b]	ee of **2** (%)[c]
1	**1d**	24		55 (89)[d,e]	51:11	
2	**1d**[f]	9	(*S*,*S*)-L$_1$ (0.55)	87 (95)[d]	>50:1	75
3	**1d**	24	(*S*,*S*)-L$_1$ (0.22)	78 (91)[d]	46:1	71
4	**1e**[g]	4		76	7.3:1	93
5	**1e**	4	(*S*,*S*)-L$_1$ (0.22)	91	24:1	97
6	**1e**	12	(*R*,*R*)-L$_1$ (0.22)	54	1.3:1	87
7	**1f**[g]	5		86	8:1	98.3
8	**1f**	5	(*S*,*S*)-L$_1$ (0.22)	94	34:1	99.3
9	**1f**	12	(*R*,*R*)-L$_1$ (0.22)	56	1.3:1	98.3

[a] Unless otherwise indicated, all reactions were carried out at room temperature in CH_2Cl_2 with 0.1−0.2 mmol of substrate and 0.2 equiv of Cu(OTf)$_2$. [b] ^{1}H NMR yield with α-methyl stilbene as the internal standard. Ratio of **2** and **3** was determined by ^{1}H NMR analysis of crude products. Compounds **2** and **3** were separable by flash column chromatography. [c] Enantiomeric excess of **2** was determined by HPLC analysis using a Chiral OD or AD column. Relative configuration of **2d** was determined by the analysis of NOESY spectra of its diol derivative (see Supporting Information), but its absolute configuration was not determined. Absolute configurations of **2e**/**2f** as (1*R*,2*R*,5*R*)- and **3e**/**3f** as (1*S*,2*S*,5*R*)- were determined by NOESY analysis. [d] Percentage conversion in parentheses. [e] Byproduct **4d** was isolated in 27% yield. [f] Performed with 0.5 equiv of Lewis acid. [g] Ee values of **1e** and **1f** were not determined.

(8) For studies on the counterion effects of copper(II) complexes, see: Evans, D. A.; Murry, J. A.; Van Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798−800.

(9) Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541−4544.

(10) Same catalyst gave excellent enantioselectivity in the *intermolecular* carbonyl ene reactions; see refs 1f,j and 13a.

(11) Evans, D. A.; Sweeney, Z. K.; Rovis, T.; Tedrow, J. S. *J. Am. Chem. Soc.* **2001**, *123*, 12095−12096.

(12) For discussion on the metal center geometry of chiral bis(oxazoline)-copper(II) complexes, see: (a) Johannsen, M.; Jørgensen, K. A. *J. Org. Chem.* **1995**, *60*, 5757−5762. (b) Evans, D. A.; Johnson, J. S.; Burgey, C. S.; Campos, K. R. *Tetrahedron Lett.* **1999**, *40*, 2879−2882. (c) Thorhauge, J.; Roberson, M.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2002**, *8*, 1888−1898.

The $Cu(OTf)_2$-catalyzed cyclization reactions of chiral substrate **1e**, prepared from commercially available (*R*)-(+)-citronellic acid (98%), gave a mixture of **2e** and **3e** in the absence of a ligand, with **2e** as the major product in 76% yield and 93% ee (entry 4). When the Lewis acid was combined with chiral ligand (*S*,*S*)-Ph-box, not only the diastereomeric ratio of **2e** to **3e** was improved but also the ee value of **2e** was enhanced (entries 4 vs 5). However, when the Lewis acid was combined with the enantiomeric ligand (*R*,*R*)-Ph-box, both the diastereomeric ratio and the ee value decreased (entry 6). Similar results were obtained for the cyclization of **1f**, another chiral substrate with a benzyl ester group. When $Cu(OTf)_2$ alone was employed as the Lewis acid, cyclization of **1f** gave a mixture of diastereomers in a 8:1 ratio with **2f** as the major product in 86% yield and 98.3% ee (entry 7). The diastereoselectivity (dr 34:1) and the enantioselectivity (99.3% ee) of **2f** were improved in the presence of chiral ligand (*S*,*S*)-Ph-box (entry 8), whereas the addition of chiral ligand (*R*,*R*)-Ph-box led to a dramatic decrease in the diastereomeric ratio (dr 1.3:1; entry 9). These results demonstrated that chiral substrates 3-(*R*)-methyl-substituted α-keto esters **1e** and **1f** matched well with $[Cu((S,S)\text{-Ph-box})](OTf)_2$ but did not match with $[Cu((R,R)\text{-Ph-box})](OTf)_2$.

The following model is proposed to account for the high stereoselectivity (Figure 2). Considering the steric interactions between the ester group and the 3-methyl group, transition state **C** would be more favored over transition state **D**. Therefore, in the absence of ligand, ene cyclization should give **2e**/**2f** as the major product and **3e**/**3f** as the minor one. However, in the presence of chiral ligand, due to the lack of steric interactions between substituents on the olefinic double bond and the phenyl group of the ligand, transition state **C** matched well with (*S*,*S*)-Ph-box (transition state **E**) but not with (*R*,*R*)-Ph-box (not shown); this led to the predominant formation of the cyclization product **2e**/**2f** with (1*R*,2*R*,5*R*)-configuration.

In conclusion, we have reported mild, efficient, and highly enantioselective carbonyl ene cyclization reactions of α-keto esters. This catalytic enantioselective method provides an easy entry to optically active *cis*-1-hydroxyl-2-alkyl esters, the chiral fragments of many natural products.[13] The applications of this method in enantioselective total synthesis of natural products will be explored.

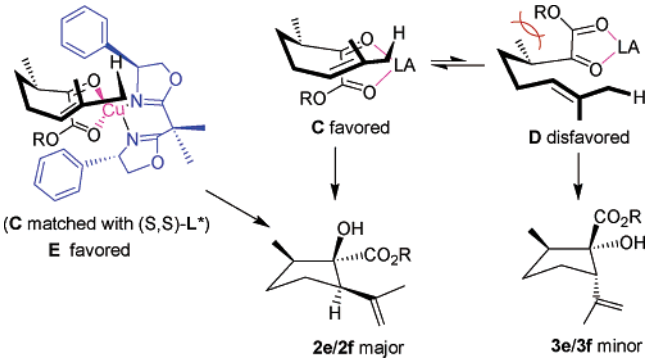


Figure 2. Proposed transition-state model for the (Cu-Ph-box) chiral Lewis acid-promoted carbonyl ene cyclization reactions of **1e**/**1f**.

Acknowledgment. This work was supported by The University of Hong Kong and Hong Kong Research Grants Council. D.Y. acknowledges the Bristol-Myers Squibb Foundation for an Unrestricted Grant in Synthetic Organic Chemistry and the Croucher Foundation for a Croucher Senior Research Fellowship Award.

Supporting Information Available: Experimental details and spectroscopic and analytical data for new compounds; determination of the relative configurations of products **2d**−**f** and **3e**,**f**; HPLC analysis of enantiomeric excesses of products **2c**−**f**; and X-ray structural analysis of *p*-bromobenzene sulfonate derivative of **2c** containing tables of atomic coordinates, thermal parameters, and bond lengths and angles. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035486D

(13) (a) Shiobara, K. Y.; Asakawa, Y.; Kodama, M.; Takemoto, T. *Phytochemistry* **1986**, *25*, 1351−1353. (b) Hubner, G.; Volkl, W.; Francke, W.; Dettner, K. *Biochem. Syst. Ecol.* **2002**, *30*, 505−523. (c) Honda, T.; Ishige, H.; Tsubuki, M.; Naito, K.; Suzuki, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 954−955.