C_2-Symmetric Copper(II) Complexes as Chiral Lewis Acids. Catalytic Enantioselective Aldol Additions of Silylketene Acetals to (Benzyloxy)acetaldehyde

David A. Evans,* Jerry A. Murry, and Marisa C. Kozlowski

Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138

Received March 5, 1996

The Lewis acid-catalyzed addition of enolsilanes to aldehydes, commonly known as the Mukaiyama aldol reaction,[1,2] is an important variant of the general aldol process. This reaction has become the focal point for the development of enantioselective variants through catalysis by chiral Lewis acids.[3] In this communication we document the use of copper(II) complexes as effective enantioselective catalysts for this process where the catalyst activates specific aldehydes through bidentate coordination, an organizational feature not common to the chiral catalysts previously reported for this process.[3]

We have recently demonstrated that bidentate coordinating bis(oxazolinyl) Cu(II) complexes **1** function as effective chiral Lewis acids in the Diels−Alder reaction of acrylimide dienophiles[4] and that tridentate bis(oxazolinyl)pyridine (pybox)[5] Cu(II) complexes **2** catalyze the analogous reaction with aldehyde dienophiles (Scheme 1).[6] These catalysts have now been applied to the aldol reaction of (benzyloxy)acetaldehyde with a range of silylketene acetals. This aldehyde was chosen on the assumption that effective catalyst−substrate organization might be achieved through bidentate chelation to the aldehyde substrate. In our initial survey, the addition of silylketene acetal **3a** to **(**benzyloxy)acetaldehyde was catalyzed by Cu(II) complexes **1a**,**b** and **2a**,**b** (eqs 1 and 2). Although both catalysts proved to be highly enantioselective, the exceptional levels of asymmetric induction exhibited by the phenyl-substituted pybox complex **2b**[7] which afforded **4a** in 99% ee and 100% yield (5 mol % **2b**, −78 °C, CH_2Cl_2, 15 min) prompted us to select this complex for further development. Upon optimization, 0.5 mol % of catalyst **2b** at 1 M concentration of aldehyde was found to catalyze the reaction in 12 h without compromising the yield or enantiomeric purity.

The reaction was found to be quite general with respect to the silylketene acetal structure (Table 1).[8] The enolsilanes derived from *tert*-butyl thioacetate, ethyl thioacetate, and ethyl acetate provided the respective β-hydroxy esters **4a**−**c** in 98−99% ee. In a related reaction, dioxolinone derivative **3d**[9] provided the corresponding adduct **4d** in 92% ee and 94% yield.[10] Extension of the reaction to Chans diene[11] afforded, after reduction with $Me_4NBH(OAc)_3$,[12] the *anti* diol **4e** (15:1 *anti:syn*) in 97% ee. This synthetically valuable diol can be purified by recrystallization to give the pure *anti* diolester as a single enantiomer. Finally, substituted enolsilanes may also be employed. For example, the (*Z*)-propionate derived silylketene

Scheme 1

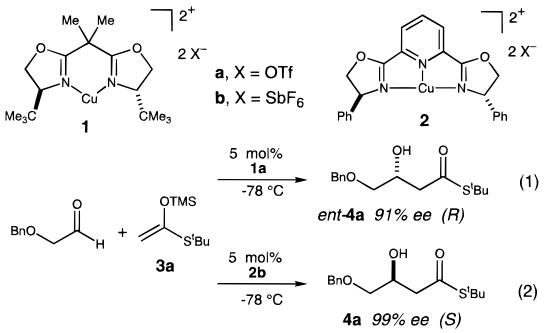


Table 1. Catalyzed Enantioselective Aldol Reactions between α-(Benzyloxy)acetaldehyde and Representative Enolsilanes

nucleophile	product	% yield	mol% **2b**	% ee[a]
3a R = S^{t}Bu	**4a** R = S^{t}Bu	100	0.5	99[b]
3b R = SEt	**4b** R = SEt	95	0.5	98[b]
3c R = OEt	**4c** R = OEt	99[c]	0.5	98[d]
3d	**4d**	94	5	92[d]
3e	**4e** *anti:syn* 15:1[f]	98	0.5	97[d,e]
3f (95:5 *Z:E*)	**4f** *syn:anti* 97:3	90	10	97[b,e]
3f (1:99 *Z:E*)	**4f** *syn:anti* 86:14	48	10	85[b,e]
3g	**4g** *syn:anti* 96:4	95	10	95[e]

[a] Enantiomeric excess determined by HPLC using a Chiracel ODH column. [b] Absolute configurations assigned by comparison of optical rotation to literature values (see ref. 3c). [c] Silyl ether cleaved with TBAF/THF to prevent retroaldol reaction. [d] Absolute configuration assigned by independent synthesis (see supporting information). [e] Values refer to the enantiomeric excess of the major diastereomer. [f] The aldol adduct was treated with $Me_4N(AcO)_3BH$ to form the *anti* diol ester.

(1) (a) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011−4. (b) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503−9.

(2) (a) Gennari, C. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, Chapter 2.4. (b) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: San Diego, CA, 1984; Vol. 3, Chapter 2. (c) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23−32.

(3) (a) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837−8. (b) Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363−4. (c) Mikami, K.; Matsukawa, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 4077−8. (d) Kobayashi, S.; Uchiro, H.; Shiina, I.; Mukaiyama, T. *Tetrahedron* **1993**, *49*, 1761−72. (e) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907−10. (f) Parmee, E. R.; Hong, Y.; Tempkin, O.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 1729−32. (g) Kiyooka, S.; Kaneko, Y.; Kume, K. *Tetrahedron Lett.* **1992**, *33*, 4927−30. (h) Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem Soc.* **1991**, *113*, 1041−2. (i) Permee, E. R.; Tempkin, O.; Masamune, S.; Abiko, A. *J. Am. Chem. Soc.* **1991**, *113*, 9365−6.

(4) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460−1.

(5) Nishiyama, H.; Kondo, M.; Nakamura, T.; Itoh, K. *Organometallics* **1991**, *10*, 500−8.

(6) Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798−800.

(7) Other substituted pybox complexes gave lower enantioselectivity: *tert*-butyl pybox (9% ee), isopropyl pybox (85% ee), benzyl pybox (67% ee).

(8) Catalyst **2b** was prepared by mixing phenyl pybox (1.0 equiv) $CuCl_2$ (1.0 equiv) and $AgSbF_6$ (2.0 equiv) in CH_2Cl_2 at room temperature for 4 h followed by filtration through a cotton plug. The resulting solution is stable to air and moisture and may be stored for up to 1 week without any special precautions. (Benzyloxy)acetaldehyde (0.50 mmol) and silylketene acetal (0.60 mmol) were added sequentially to a 12.5 mM solution of **2b** at −78 °C. After the reaction was complete (≤12 h), the mixture was filtered through silica and the silyl ether was hydrolyzed with 1 N HCl in THF to yield the hydroxy ester.

(9) Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Chem. Pharm. Bull.* **1994**, 42, 839−45.

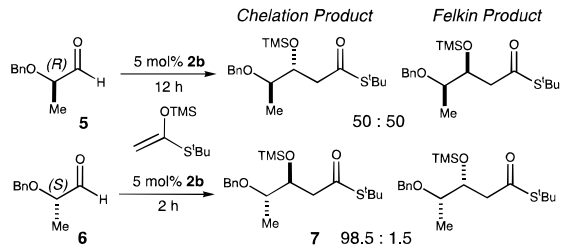
(10) The addition of this nucleophile to aldehydes has recently been reported. See: Singer, R. A.; Carriera, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 12360−12361.

(11) Brownbridge, P.; Chan, T. H.; Brook, M. A.; Kang, G. J. *Can. J. Chem.* **1983**, *61*, 688−93.

(12) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988,** *110*, 3560−78.

S0002-7863(96)00712-3 CCC: $12.00

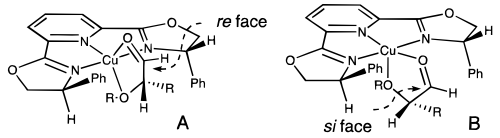
Scheme 2



acetal **3f** provided the *syn* aldol adduct **4f** in high diastereo- and enantioselectivity (97:3 *syn:anti*, *syn* 97% ee). On the other hand, the corresponding (*E*)-propionate silylketene acetal **3f** proved to be a much poorer substrate, giving lower conversion and selectivity (86:14 *syn:anti*, *syn* 85% ee). The geometric requirement for disposing the alkyl and OTMS moieties in an *anti* orientation for optimal enantioselectivity is also evident in the analogous reaction of the silylketene acetal **3g** which also affords a highly selective aldol reaction with good control at both stereogenic centers.

We next investigated the scope of the reaction with respect to the aldehyde component. Reactions with benzaldehyde and dihydrocinnamaldehyde were nonselective. Apparently the requirement for a chelating substituent on the aldehyde partner is critical to catalyst selectivity, as α-(*tert*-butyldimethylsiloxy)-acetaldehyde gave diminished enantioselectivity (56% ee). Interestingly, *β*-(benzyloxy)propionaldehyde provided racemic product, indicating a strict requirement for a five-membered catalyst−aldehyde chelate.

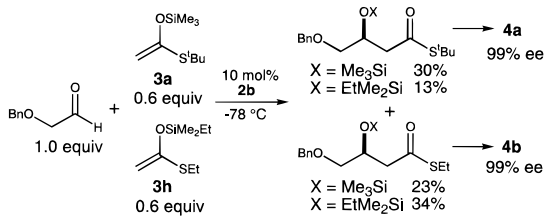
Stereochemical models of the catalyst−RCHO complex in the two probable penta-coordination geometries (square pyramidal or trigonal bipyramidal) are illustrated below.[13] In the symmetric trigonal bypyramidal model **A** (R = H), the *si*



aldehyde enantioface is masked by the ligand phenyl group exposing the *re* enantioface to nucleophilic attack. In the alternate square pyramidal complex **B** (R = H) the *re* aldehyde enantioface is shielded.[14] Since enantioselective formation of *(S)-β*−hydroxy esters is observed in all cases (*si* facial attack), the absolute stereochemistry of the products is consistent with the proposed square pyramidal coordination model. Additional support for this proposed RCHO−catalyst geometry has been obtained from ESR spectroscopy which indicates that the copper geometry is unequivocally square pyramidal.[15]

Double stereodifferentiating experiments with (*R*)- and (*S*)-α-(benzyloxy)propional (**5**) and (**6**) have been carried out to provide further support for the catalyst−RCHO model (Scheme 2). It has been well established that bidentate chelation between the =O and OBn moieties will reverse the inherent Felkin aldehyde diastereoface selectivity with this substrate.[16] In the mismatched experiment, **5** afforded a poorly selective, slow reaction. This result is consistent with catalyst−RCHO square

Scheme 3



pyramidal coordination where substrate (Me) and ligand (Ph) substituents mask *opposite* RCHO enantiofaces. On the other hand, **6** underwent rapid reaction providing a 98.5:1.5 mixture of diastereomers favoring the chelation-controlled product **7**. In the square pyramidal complex **B** (R = Me), the methyl substituent in **6** reinforces the facial bias imposed by the catalyst. A corollary to this experiment is that **5** is predicted to be a catalyst inhibitor. This has also been shown to be the case. While these results are consistent with the square pyramidal model **B** (R = Me), a trigonal bipyramidal model **A** (R = Me) *would predict the opposite matched and mismatched relationships*.

The silyl transfer component of the reaction has also been investigated. Silicon transfer from the initially formed catalyst−Nu−RCHO complex may proceed via intramolecular or intermolecular processes. It has been reported that intermolecular silyl transfer results in a catalytically competent silicon intermediate which affords an avenue for a competing achiral catalytic process that may compete with the enantioselective variant.[17] We have investigated this possibility in the present system by employing a mixture of two different silylketene acetals which should exhibit similar reactivities (Scheme 3). Treatment of 0.6 equiv each of silylketene acetals **3a** and **3h** with 1.0 equiv of (benzyloxy)acetaldehyde and 10 mol % of catalyst **2b** afforded significant quantities of the four possible products as detected by GLC analysis.[18] Deprotection of the silyl ethers and chiral HPLC analysis of the derived alcohols indicated that both aldol adducts **4a** and **4b** were enantiomerically pure (99% ee). Accordingly, we conclude that although there is a large intermolecular silyl transfer component in the reaction, the transient silyl species which we speculate might be R_3SiSbF_6[19] does not compete effectively at −78 °C with the copper catalyst in this aldol reaction.

In conclusion, we have documented an efficient, catalytic, enantioselective addition of silylketene acetal nucleophiles to (benzyloxy)acetaldehyde utilizing the C_2-symmetric bis(oxazolinyl)pyridine Cu(II) complex **2b**. Further studies to address the scope of these reactions and the coordination chemistry of related complexes will be forthcoming.

Acknowledgment. Financial support was provided by the National Science Foundation and the National Institutes of Health. Fellowships from the National Institutes of Health (J.A.M.) and the National Science Foundation (M.C.K.) are gratefully acknowledged. We would like to thank Professor William Tolman (University of Minnesota) for helpful discussions concerning the ESR experiments. The NIH BRS Shared Instrumentation Grant Program 1-S10-RR04870 and the NSF (CHE 88-14019) are acknowledged for providing NMR facilities.

Supporting Information Available: Experimental procedures and spectral data, including ESR spectra, for all compounds (6 pages). Ordering information is given on any current masthead page.

JA960712I

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

(14) In the square pyramidal geometry, the strong coordinating site resides in the ligand plane with a weaker coordination site in the axial position. For maximal RCHO activation, we presume that carbonyl coordination occurs in the ligand plane.

(15) The ESR data were obtained at 132 K and 9.4 GHz. The Hamiltonian spin parameters are: $g_\perp = 2.09$, $g_\parallel = 2.28$, and $A_\parallel = 180.2$ G. The ratio of $g_\parallel/A_\parallel$ is indicative of distortion away from square pyramidalization: a value of 126×10^4 is consistent with negligible amounts of distortion. See: (a) ref 13, page 662. (b) Batra, G.; Mathur, P. *Transition Met. Chem.* **1995**, *20*, 26−9.

(16) Gennari has shown that the $SnCl_4$-mediated addition of **3a** to α-(benzyloxy)propionaldehyde provides the chelation-controlled *anti* adduct (98:2 *anti*:*syn*). Gennari, C.; Cozzi, P. G. *Tetrahedron* **1988**, *44*, 5965−74.

(17) (a) Hollis, T. K.; Bosnich, B. *J. Am. Chem. Soc.* **1995**, *117*, 4570−81. (b) Carreira, E. M.; Singer, R. A. *Tetrahedron Lett.* **1994**, *35*, 4323−6.

(18) The appropriate control experiments were performed ruling out catalyst-promoted silicon scrambling of the silylketene acetals or of the product silyl ethers.

(19) Olah, G. A.; Heiliger, L.; Li, X.-Ya; Prakash, G. K. S. *J. Am. Chem. Soc.* **1990**, *112*, 5991−5995.