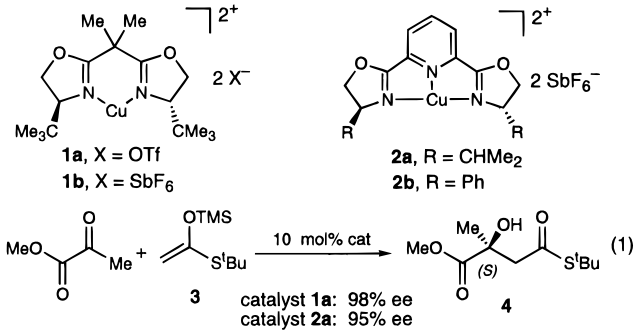
C_2-Symmetric Copper(II) Complexes as Chiral Lewis Acids. Catalytic Enantioselective Aldol Additions of Enolsilanes to Pyruvate Esters

David A. Evans,* Marisa C. Kozlowski,
Christopher S. Burgey, and David W. C. MacMillan

Department of Chemistry and Chemical Biology
Harvard University, Cambridge, Massachusetts 02138

Received May 12, 1997

Our laboratory has been engaged in the development of chiral Cu(II)-based Lewis acids that exhibit the capacity to catalyze enantioselective Diels−Alder[1] and aldol reactions[2] with substrates that can participate in catalyst chelation. In our recent study,[2] we reported that bidentate bis(oxazolinyl) (box) and tridentate bis(oxazolinyl)pyridyl (pybox)[3] Cu(II) complexes **1** and **2** are effective chiral Lewis acid catalysts in the aldol reactions of benzyloxyacetaldehyde with enolsilanes. In this communication, we demonstrate that these complexes also mediate the enantioselective additions of enolsilanes to 1,2-dicarbonyl compounds, to provide functionalized succinate derivatives, useful synthons in natural product synthesis.[4] Although excellent stereocontrol in these reactions may be achieved through the use of stoichiometric chiral ester controllers and chiral metal complexes, to our knowledge, this is the first report of a catalytic enantioselective addition of enolsilanes to pyruvate esters.[5,6]

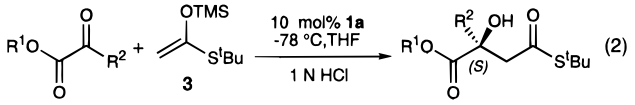


An evaluation of ligand architecture[7] for the addition of silylketene acetal **3** to methyl pyruvate (eq 1) revealed that the (*S*,*S*)-Cu(II) complex **1a** (10 mol % catalyst, CH_2Cl_2, −78 °C, 1 h) was the most enantioselective of the box complexes affording (*S*)-**4** in high enantioselectivity and yield (98% ee, 92%).[8] The pybox-derived complexes **2** are also effective catalysts exhibiting the capacity to participate in chelation through square-pyramidal complexes (*vide infra*),[2] with the isopropyl−pybox derivative **2a** being optimal in affording (*S*)-**4** in high enantioselectivity and yield (95% ee, 92%) under the same conditions.[9] In a comparison of the complexes derived from the bi- and tridentate ligands, the *tert*-butyl−box derived catalyst **1a** was found to tolerate a somewhat wider variety of substrates (*vide infra*), and as such, was selected for further exploration. Counterion selection is also critical for reaction optimization. For example, the analogous box−SbF_6 complex **1b** was both more reactive and less enantioselective (75% ee) than its triflate counterpart **1a**, whose Lewis acidity is attenuated by "counterion buffering".

The effect of reaction solvent and temperature on enantioselection and yield was then evaluated. The reaction of methyl pyruvate with **3** catalyzed by the box complex **1a** (eq 1) was found to proceed with high enantioselectivity and good yield in a variety of solvents (THF, Et_2O, 99% ee; CH_2Cl_2, 98% ee; $PhCH_3$, 96% ee). Further studies revealed that THF was the optimal solvent for catalyst **1a**, allowing the use of low catalyst loadings (eq 1, 1 mol % **1a**, 99% ee, 96% yield, 2 h).[10] The favorable enantioselectivity/temperature profile (eq 1) found with catalyst **1a** (THF, −78 °C, 99% ee; +20 °C, 92% ee) corresponds to the profile that has also been observed with complex **1b** in the catalysis of the Diels−Alder reaction.[1d]

Those experiments that probe the scope of the α-keto ester reaction component are summarized in Table 1. Excellent

Table 1. Catalyzed Enantioselective Aldol Reactions between **3** and Representative Pyruvates (Eq 2)



entry	R^1	R^2	% ee[a]	% yield
1	Me	Me	99[b]	96
2	Bn	Me	99[b]	95
3	tBu	Me	99[c]	91
4	Me	Et	94[c]	84
5	Me	iBu	94[c]	94
6	Et	iPr	36[c]	84

[a] Enantiomeric excess determined by HPLC with use of a Chiralcel OD-H column. [b] Absolute configurations assigned by conversion to dimethyl citramalate (see Supporting Information). [c] Absolute configuration assigned by analogy.

(1) (a) Evans, D. A.; Miller, S. J.; Lectka, T. C. *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.; Kozlowski, M. C.; Tedrow, J. S. *Tetrahedron Lett.* **1996**, *37*, 7481−7484.

(2) Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem Soc.* **1996**, *118*, 5814−5815. For literature citations for catalyzed enantioselective aldol reactions with simple aldehydes see ref 2, footnote 3.

(3) Nishiyama, H.; Kondo, M.; Nakamura, T.; Itoh, K. *Organometallics* **1991**, *10*, 500−508.

(4) 2,3-Difunctionalized succinic acid derivatives have been incorporated into the synthesis of a number of collagenase inhibitors which may prove therapeutically useful: Schwartz, M. A.; Van Wart, H. E. *Prog. Med. Chem.* **1992**, *29*, 271−334.

(5) Examples of diastereoselective and metal-complex promoted asymmetric pyruvate Mukaiyama aldol reactions are known. Diastereoselective: (a) Jacobson, I. C.; Reddy, G. P. *Tetrahedron Lett.* **1996**, *37*, 8263−8266. (b) Akiyama, T.; Ishikawa, K.; Ozaki, S. *Synlett* **1994**, 275−276. (c) Chen, M.-Y.; Fang, J.-M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1737−1741. (d) Ojima, I.; Yoshida, K.; Inaba, S. *Chem. Lett.* **1977**, 429−432. Stoichiometric chiral metal-complex promoted: (e) Kobayashi, S.; Horibe, M.; Saito, Y. *Tetrahedron* **1994**, *50*, 9629−9642. (f) Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1992**, *57*, 1324−1326. (g) Kobayashi, S.; Fujishita, Y.; Mukaiyama, T. *Chem. Lett.* **1989**, 2069−2072.

(6) One catalyzed aldol addition to pyruvate esters has been reported, but it is limited to isocyanoacetate or isocyanoacetamide nucleophiles. Ito, Y.; Sawasura, M.; Hamashima, H.; Emura, T.; Hayashi, T. *Tetrahedron Lett.* **1989**, *30*, 4681−4684.

(7) Other box−$Cu(OTf)_2$ complexes afforded lower enantioselectivity: isopropyl−box (23% ee), benzyl−box (10% ee), phenyl−box (43% ee).

(8) The catalysts were prepared as previously described, see refs 1c and 2. In a representative procedure the pyruvate ester (0.50 mmol) and silylketene acetal (0.60 mmol) were added sequentially to a catalyst solution in the indicated solvent (1.5−2.0 mL, 0.05 mmol, 10 mol %) at −78 °C. After the reaction was complete (0.5−24 h), the mixture was filtered through silica with Et_2O and the silyl ether was hydrolyzed with 1 N HCl in THF to yield the hydroxy ester, which was purified by flash chromatography.

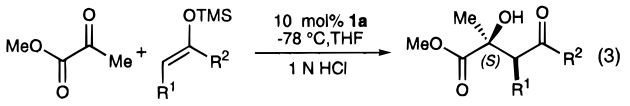
(9) Other pybox−$Cu(SbF_6)_2$ complexes gave lower enantioselectivity: *tert*-butyl−pybox (4% ee), benzyl−pybox (77% ee), phenyl−pybox (62% ee). The reaction with the isopropyl pybox−$Cu(OTf)_2$ catalyst gave the product in 61% ee.

(10) Typically the catalyst was generated by stirring the bis(oxazolinyl) ligand and $Cu(OTf)_2$ (Aldrich) in THF for 1 h at room temperature to yield a homogeneous emerald-green solution. Shorter or longer complexation times did not alter the efficacy as long as complete dissolution of the solid metal triflate (≥15 min) had occurred. The catalyst solution must be kept rigorously anhydrous. The development of a deep blue solution is indicative of the formation of the bis(aquo) complex. These reactions are exothermic. In large-scale reactions (>10 mmol) the use of an internal temperature probe and regulated addition of the silylketene acetal component (∼2−20 min) to maintain temperature control is recommended.

S0002-7863(97)01521-7 CCC: $14.00

enantioselectivities were observed with box complex **1a** in the reactions of silylketene acetal **3** with benzyl and *tert*-butyl pyruvate (entries 2,3, 99% ee), suggesting that the stereochemical course of this process is tolerant of the nature of the ester substituent (R^1, eq 2). It appears that high enantioselection is observed (≥94% ee) when the acyl substituent R^2 is either primary or β-branched (Me, Et, ^{i}Bu, entries 3−5), but more sterically demanding substituents impair enantioselection (entry 6, $R^2 = {}^i$Pr, 36% ee).

Table 2. Catalyzed Enantioselective Aldol Reactions between Methyl Pyruvate and Representative Enolsilanes (Eq 3)

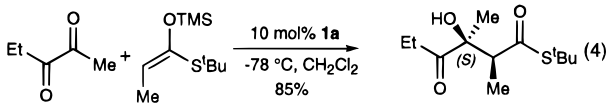


entry	R^1	R^2	enol silane geometry[a]	syn:anti[b,c] ratio	% ee[b,c]	% yield
1	H	EtS			97	97 (100)[d]
2	H	Ph			99	77
3	H	Me			93	76[e]
4	Me	^{t}BuS	(*Z*)	94:6	96	96[f]
5	Me	^{t}BuS	(*E*)	95:5	98	88[f,g]
6	Me	EtS	(*Z*)	94:6	93	90
7	Me	EtS	(*E*)	98:2	98	91
8	^{i}Bu	EtS	(*Z*)	90:10[h]	93[h]	88[f]

[a] Isomeric purity ≥90%. [b] Product ratios determined by HPLC with use of a Chiralcel OD-H column. [c] Relative and absolute stereochemistry determined by independent synthesis (see Supporting Information). [d] Reaction performed on a 50-mmol scale with 1 mol % **1a**. [e] Reaction performed with benzyl pyruvate. [f] Reaction performed in CH_2Cl_2. [g] Reaction required 0.9 equiv of TMSOTf for complete conversion. [h] Configuration assigned by analogy.

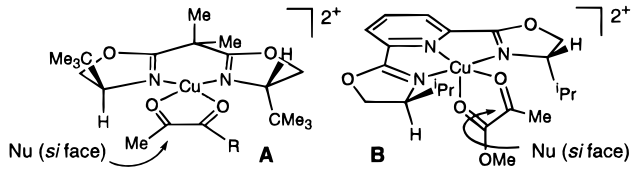
Significant structural variation in the enolsilane component is possible without loss in enantioselectivity (Table 2). Both silylketene acetals and ketone-derived enolsilanes afford highly enantioselective additions (entries 1−3, ≥93% ee). The catalyzed addition of substituted silylketene acetals to pyruvate esters in the presence of the box complex **1a** provides succinate derivatives with high *syn* diastereoselectivity (eq 3, Table 2, R^1 = Me, ^{i}Bu). The (*Z*) and (*E*) isomers of the illustrated silylketene acetals (entries 4−7) react in a stereoconvergent manner, providing the *syn* aldol adducts in high diastereo- and enantioselectivity (≥94:6 *syn*:*anti*, ≥93% ee). It appears that the *syn* diastereoselectivity observed in this reaction is not ligand dependent since pybox complex **2a** also exhibits the same stereochemical bias in the catalysis of these processes. It is noteworthy that pybox complex **2b** also mediates a highly *syn* diastereoselective addition of a range of substituted enolsilanes to benzyloxyacetaldehyde.[2] Finally, to demonstrate the preparative utility of this methodology, the reaction of methyl pyruvate with the silylketene acetal of ethyl thioacetate (eq 3) was conducted on a 50-mmol scale employing 1 mol % of the box catalyst **1a** (Table 2, entry 1) to generate the desired adduct in quantitative yield while maintaining high enantioselectivity (97% ee).[10] While trimethylsilyl triflate (TMSOTf) is frequently a liability in the execution of enantioselective aldol reactions catalyzed by metal triflate−ligand complexes due to the fact that this reagent is also an effective reaction catalyst,[11] it is interesting to note that TMSOTf generally *accelerates* these reactions without degrading enantioselectivity. This observation is useful for certain hindered cases (Table 2, entry 5). The role of this addend has not yet been precisely defined; however, we tentatively conclude that TMSOTf is facilitating the slow step in the catalytic cycle, catalyst turnover, by silylation of the intermediate copper aldolate. Independent control experiments confirm that TMSOTf is not a competitive catalyst for these processes.

The Cu(II) complex **1a** can also be employed to catalyze additions to unsymmetrical vicinal diketones (eq 4). The principal issue in this reaction is that of relative carbonyl reactivity differentiated by the subtle methyl vs ethyl substitution at the two reaction centers. In spite of the modest bias for reaction at the MeCO−moiety (1.4:1) in the addition catalyzed by $TiCl_4$ (−78 °C, CH_2Cl_2), the reaction of the (*Z*) silylketene acetal derived from *tert*-butyl thiopropionate with 2,3-pentanedione catalyzed by **1a** proceeds with high regioselectivity (98:2), diastereoselectivity (93:7), and enantioselectivity (97% ee).



regioselection, 98:2; diastereoselection, 93:7; enantioselection, 97% ee

Enantioselective formation of the (*S*)-hydroxy succinates was observed in all cases from both (*S*,*S*)-box and (*S*,*S*)-pybox complexes. In analogy to our Diels−Alder studies with complex **1**,[1a] the sense of induction can be rationalized by invoking a square-planar Cu(II)box intermediate in which the pyruvate carbonyl oxygens chelate to the copper center (model A, R = OMe).[12,13] EPR spectroscopic studies of solutions of complex **1a** and methyl pyruvate provide further support for this substrate−catalyst geometry.[14] The sense of asymmetric induction that is observed in the (*S*,*S*)-pybox complex **2a** is consistent with the formation of the illustrated five-coordinate square-pyramidal complex (Model B).[15] By inspection, the *si* face in both substrate−catalyst complexes is accessible to nucleophilic attack. Model A (R = Et) is also consistent with the stereochemical course of the 2,3-pentanedione addition reactions (eq 4). 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 NSF and the NIH. Fellowships from the National Science Foundation (M.C.K.) and the American Cancer Society (C.S.B.) are gratefully acknowledged. The NIH BRS Shared Instrumentation Grant Program 1-S10-RR04870 and the NSF (CHE 88-14019) are acknowledged for providing NMR facilities. Amino alcohols were generously provided by NSC Technologies.

Supporting Information Available: Experimental procedures, spectral data for all compounds, and stereochemical proofs (10 pages). See any current masthead page for ordering and Internet access instructions.

JA971521Y

(11) (a) Hollis, T. K.; Bosnich, B. *J. Am. Chem. Soc.* **1995**, *117*, 4570−4581. (b) Carreira, E. M.; Singer, R. A. *Tetrahedron Lett.* **1994**, *35*, 4323−4326. (c) Denmark, S. E.; Chen, C. T. *Tetrahedron Lett.* **1994**, *35*, 4327−4330.

(12) For the sake of the ensuing analysis, it is assumed that both triflate ligands are dissociated from the metal center. For maximal activation, we presume that substrate coordination occurs in the ligand plane at the two strongest coordinating sites.

(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) The EPR data indicate a strong square-planar pattern, which is consistent with either a square-planar or square-pyramidal copper geometry. See Supporting Information.

(15) In the square-pyramidal geometry, the strong coordinating site resides in the ligand plane with a weaker coordination site in the axial position. Although two diastereomeric substrate catalyst complexes should be expected, we presume that the complex with the ketone carbonyl coordinated in the equatorial plane is the complex that leads to product.