C_2-Symmetric Copper(II) Complexes as Chiral Lewis Acids. Scope and Mechanism of Catalytic Enantioselective Aldol Additions of Enolsilanes to (Benzyloxy)acetaldehyde

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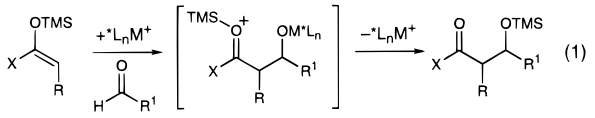
Abstract: C_2-Symmetric bis(oxazolinyl)pyridine (pybox)−Cu(II) complexes have been shown to catalyze enantioselective Mukaiyama aldol reactions between (benzyloxy)acetaldehyde and a variety of silylketene acetals. The aldol products are generated in high yields and in 92−99% enantiomeric excess using as little as 0.5 mol % of chiral catalyst [Cu((*S*,*S*)-Ph-pybox)]$(SbF_6)_2$. With substituted silylketene acetals, syn reaction diastereoselection ranging from 95:5 to 97:3 and enantioselectivities ≥95% are observed. Investigation into the reaction mechanism utilizing doubly labeled silylketene acetals indicates that the silyl-transfer step is intermolecular. Further mechanistic studies revealed a significant positive nonlinear effect, proposed to arise from the selective formation of the [Cu((*S*,*S*)-Ph-pybox)((*R*,*R*)-Ph-pybox)]$(SbF_6)_2$ 2:1 ligand:metal complex. A stereochemical model is presented in which chelation of (benzyloxy)acetaldehyde to the metal center to form a square pyramidal copper intermediate accounts for the observed sense of induction. Support for this proposal has been obtained from double stereodifferentiating reactions, EPR spectroscopy, ESI spectrometry, and, ultimately, the X-ray crystal structure of the aldehyde bound to the catalyst. The C_2-symmetric bis(oxazolinyl)−Cu(II) complex [Cu((*S*,*S*)-*tert*-Bu-box)]$(OTf)_2$ is also an efficient catalyst for the aldol reaction, but the scope with this system is not as broad.

Introduction

The development of a general enantioselective aldol addition reaction has been an enduring problem in organic chemistry for nearly 25 years.[1] Seminal advances have been realized in the development of high levels of reaction diastereoselection, while improvements in chiral auxiliary design have led to the achievement of absolute stereochemical control for many of these reactions.[1] Nevertheless, the broad extension of high levels of diastereoselectivity and enantioselectivity to *catalytic* aldol reactions has not been trivial. The most notable achievements that have been made in this area have focused on the addition of enolsilanes to aldehydes[2] through catalysis by chiral Lewis acids (*L_nM^+, eq 1).[3] Excellent progress in the development



(1)

of enantioselective "Mukaiyama" aldol variants has been made;[4] however, no individual catalyst system developed to date tolerates substantial variation in both the nucleophilic and electrophilic components while maintaining low catalyst loading (<10 mol %). In part, the lack of structural data on many of the relevant catalyst−aldehyde complexes has inhibited further catalyst refinement. Indeed, some of the fundamental control elements for these reactions are just being revealed.

The realization of high enantioselectivity for the catalyzed aldol reaction necessarily relies on effective channeling of the reactants through a transition state that is substantially lower in energy than competing diastereomeric transition-states. For the process at hand, a high level of transition-state organization is required, necessitating control of factors that include (A) mode of binding (η^2 vs η^1) of the carbonyl group to the Lewis acid; (B) the regiochemistry of complexation to the two available C═O lone pairs; and (C) the establishment of a fixed diastereofacial bias, thereby biasing enol/enolate addition to one of the two carbonyl π-faces. The discovery of effective strategies for controlling the conformation of the Lewis acid-bound aldehyde lies at the heart of current advances in chiral catalyst design in this area. Recent investigations have sought to

(1) (a) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: San Diego, CA 1984; Vol. 3, Chapter 2. (b) Evans, D. A. *Aldrichim. Acta* **1982**, *15*, 23−32.

(2) (a) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011−1014. (b) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503−7509. (c) Gennari, C. in *Comprehensive Organic Synthesis;* Trost, B. M., Fleming, I., Eds; Pergamon Press: New York, NY, 1991; Vol. 2, Chapter 2.4.

(3) For a comprehensive review of catalytic enantioselective aldol reactions: Nelson, S. G. *Tetrahedron Asymmetry* **1998**, *9*, 357−389.

(4) (a) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *117*, 8837−8838. (b) Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363−2364. (c) Mikami, K.; Matsukawa, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 4077−4078. (d) Kobayashi, S.; Uchiro, H.; Shiina, I.; Mukaiyama, T. *Tetrahedron* **1993**, *49*, 1761−1772. (e) Corey E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907−6910. (f) Parmee, E. R.; Hong, Y.; Tempkin, O.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 1729−1732. (g) Kiyooka, S.; Kaneko, Y.; Kume, K. *Tetrahedron Lett.* **1992**, *33*, 4927−4930. (h) Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041−1042. (i) Parmee, E. R.; Tempkin, O.; Masamune, S.; Abiko, A. *J. Am. Chem. Soc.* **1991**, *113*, 9365−9366. (j) Yanagisawa, A.; Matsumoto, Y.; Nakashima, H.; Asakawa, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1997**, *119*, 9319−9320 and references therein.

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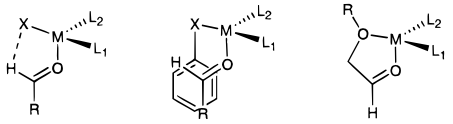
incorporate additional stabilizing interactions such as hydrogen bonding,[5] π-stacking,[4] or chelation, incorporated individually or in concert, into the catalyst−aldehyde complex to provide a highly defined carbonyl facial bias (Scheme 1). The focal point

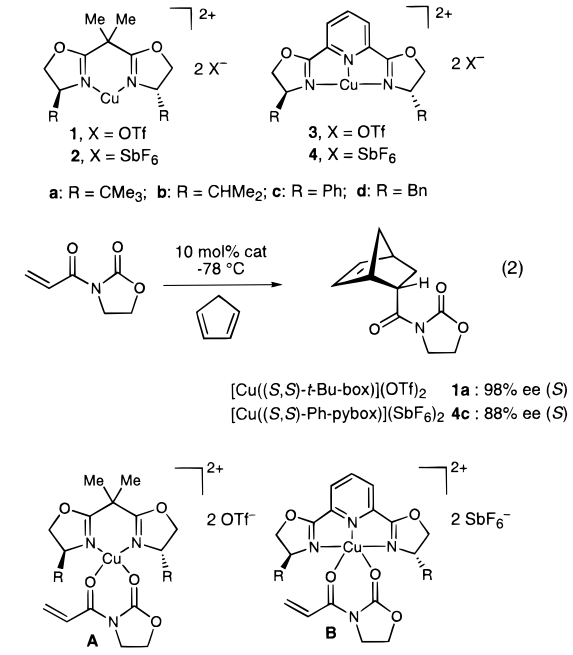
Scheme 1



of the present investigation has been to discover chiral metal complexes that exhibit a strong propensity toward substrate chelation while also meeting the other criteria necessary for their application to asymmetric catalysis of the aldol reaction.

Previous work from our laboratory has demonstrated that bidentate bis(oxazolinyl) (box) (**1** and **2**)−Cu(II) and tridentate bis(oxazolinyl)pyridine (pybox) (**3** and **4**)−Cu(II) complexes can function as effective chiral Lewis acid catalysts in the Diels−Alder reaction with substrates that can participate in catalyst chelation (Scheme 2, eq 2).[6] Further studies revealed

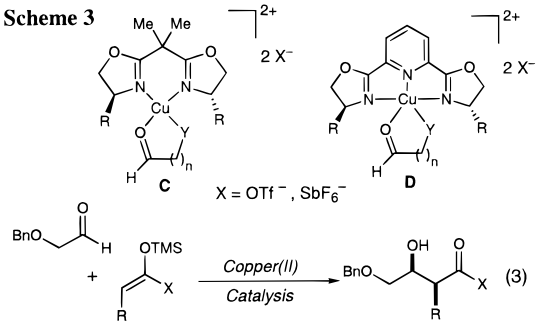
Scheme 2



that these Cu(II) catalysts maintain excellent levels of reactivity over a range of diene substrates, attesting to the high Lewis acidity of these complexes.[7]

The selectivity observed with both the Cu(II) box and pybox complexes suggested that these catalysts would also be promising candidates for the Mukaiyama aldol reaction with aldehyde substrates that could present the potential for catalyst chelation. Indeed, accumulated evidence has indicated that chelation is a critical control element in defining the catalyst−substrate architecture for the Diels−Alder reaction (Scheme 2, **A** and **B**),[6] and we postulated that extrapolation of these models to include chelating aldehydes would furnish well-defined catalyst−substrate complexes (Scheme 3, **C** and **D**). In continuing the

Scheme 3



theme of developing laboratory analogues of biosynthetic pathways,[8] (benzyloxy)acetaldehyde[9] was selected as the initial substrate to probe the utility of these Cu(II) complexes in the Mukaiyama aldol reaction (eq 3), since this aldehyde may be regarded as an equivalent to the acetate starter unit in polyacetate biosynthesis. Moreover, the benzyloxy moiety provides a convenient point for further elaboration of the resulting aldol adducts. In this article, we document the use of copper(II) complexes as effective enantioselective catalysts for the Mukaiyama aldol reaction, where the aldehyde component is activated through bidentate coordination, an organizational feature not common to chiral Lewis acids previously reported for this process;[10] furthermore, we provide direct structural evidence to support the proposed model of stereochemical induction.

Preliminary Results

Bis(oxazoline) Ligand Survey. The (*S*,*S*)-bis(oxazolinyl) copper complexes **1** and **2** were initially evaluated as catalysts in the addition of *tert*-butyl thioacetate trimethylsilylketene acetal[11] to (benzyloxy)acetaldehyde (eq 6). The bis(oxazolinyl) copper complexes **1a**−**d** were prepared by stirring a solution of the (*S*,*S*)-bisoxazoline ligand **5**[12] and $Cu(OTf)_2$ (typically 10 mol %, ∼0.03 M in catalyst) in CH_2Cl_2 (25 °C, 3 h) as

(5) (a) Corey, E. J.; Barnes-Seeman, D.; Lee, T. W. *Tetrahedron Lett.* **1997**, *38*, 1699−1702. (b) Corey, E. J.; Rohde, J. J. *Tetrahedron Lett.* **1997**, *38*, 37−40.

(6) (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. (e) Evans, D. A.; Barnes, D. M. *Tetrahedron Lett.* **1997**, *38*, 57−58. (f) Evans, D. A.; Johnson, J. S. *J. Org. Chem.* **1997**, *62*, 786−787. (g) Evans, D. A.; Shaughnessy, E. A.; Barnes, D. M. *Tetrahedron Lett.* **1997**, *38*, 3193−3194.

(7) These copper complexes are also effective enantioselective catalysts for the hetero Diels−Alder and carbonyl-ene reactions: (a) Evans, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 4895−4896. Evans, D. A.; Olhava, E. J.; Johnson, J. S.; Janey, J. M. *Angew. Chem.* **1998**, *24*, 3554−3557. (b) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824−5825.

(8) Evans, D. A.; Clark, J. S.; Novack, V. J.; Sheppard, G. S.; Metternich, R.; Ng, H. P.; Le, A.; Ennis, M. D.; Kim, A. S.; Ripin, D. H. B. *J. Am. Chem Soc.*, in press.

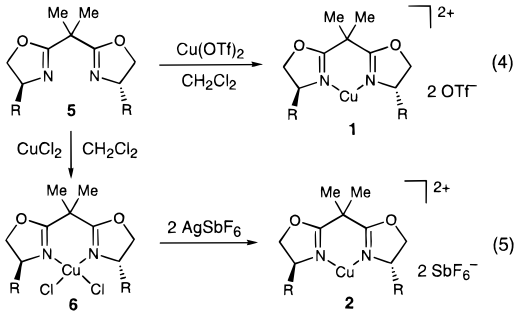
(9) (Benzyloxy)acetaldehyde is commercially available from Aldrich Chemical Co. Alternatively, an inexpensive two-step synthesis from 2-butene-1,4-diol is amenable to large-scale preparations via bis-benzylation (Garner, P.; Park, J. M. *Synth. Commun.* **1987**, *17*, 189−193), followed by ozonolysis (Danishefsky, S. J.; DeNinno, M. P. *J. Org. Chem.* **1986**, *51*, 2615−2617).

(10) A preliminary account of this work has appeared: Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814−5815.

(11) Kuwajima, I.; Kato, M.; Sato, T. *J. Chem. Soc., Chem. Commun.* **1978**, 478−479.

(12) (a) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726−728. (b) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005−6008. (c) Müller, D.; Umbricht, B. W.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232−240. (d) Denmark, S. E.; Nakajima, N.; Nicaise, J.-C.; Faucher, A. M.; Edwards, J. P. *J. Org. Chem.* **1995**, *60*, 4884−4892. (e) 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.

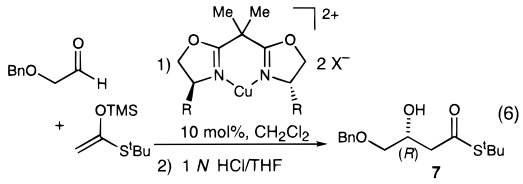
previously described (eq 4).[6a] The cationic hexafluoroantimonate complex **2a** was formed by halide abstraction from the preformed [Cu((*S*,*S*)-*tert*-Bu-box)]Cl_2 complex (**6**)[12e] with $AgSbF_6$, followed by filtration through dry Celite (or a PTFE 0.45-μm filter) to remove the precipitated AgCl (eq 5).[6c,12e]



a: R = CMe_3; **b**: R = $CHMe_2$; **c**: R = Ph; **d**: R = Bn

Addition of (benzyloxy)acetaldehyde to a cooled solution (−78 °C) of the catalyst, followed by subsequent dropwise addition of the *tert*-butyl thioacetate-derived trimethylsilylketene acetal, afforded the protected β-hydroxy ester (eq 6). Brief treatment of this silyl ether with 1 N HCl in THF produced the expected alcohol **7**, the enantioselectivity of which was assayed by chiral HPLC (Daicel OD-H column). The absolute configuration of the adduct was established by comparison of the optical rotation with that in the literature.[4c] This ligand screen revealed that the phenylglycine (Ph-box, **1c**)- and valine (*i*-Pr-box, **1b**)-derived box complexes were poorly enantioselective catalysts (Table 1, entries 1 and 2, 9% ee); however, the Cu-$(OTf)_2$ complexes of both the phenylalanine (Bn-box, **1d**) and *tert*-leucine (*tert*-Bu-box, **1a**) bisoxazolines delivered the aldol adduct with high enantioselectivity (entries 3 and 4). Use of the corresponding hexafluoroantimonate complex [Cu((*S*,*S*)-*tert*-Bu-box)]$(SbF_6)_2$ (**2a**), the optimal catalyst for the Diels−Alder reaction, afforded the (*S*) product with only modest enantioselectivity (Table 1, entry 5, ≤64% ee).

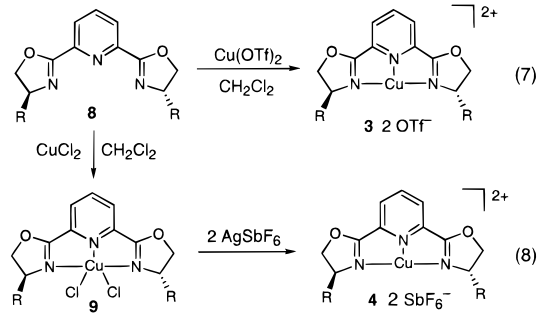
Table 1. Effect of Ligand and Counterion in the Catalyzed Benzyloxyacetaldehyde Aldol Reaction (eq 6)



entry	R	X	time (-78 °C)	% ee[a]
1	Ph	OTf (**1c**)	15 min	9 (*R*)
2	$CHMe_2$	OTf (**1b**)	15 min	9 (*S*)
3	Bn	OTf (**1d**)	60 min	88 (*R*)
4	CMe_3	OTf (**1a**)	60 min	91 (*R*)
5	CMe_3	SbF_6 (**2a**)	15 min	≤64 (*S*)

[a]Enantiomeric excess determined by HPLC using a Chiralcel OD-H column. Absolute configuration determined by comparison of the optical rotation to literature values.

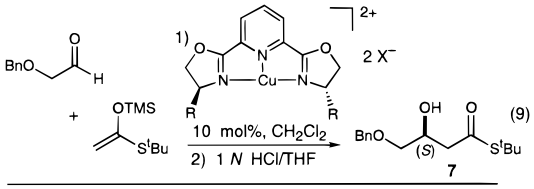
Pyridine(bisoxazoline) Ligand Survey. Dichloromethane solutions of the (*S*,*S*)-pybox ligands **8**[13] were complexed with $Cu(OTf)_2$ to form blue solutions of the chiral triflate complexes **3a**−**d** (eq 7). Preparation of the cationic [Cu((*S*,*S*)-pybox)]-$(SbF_6)_2$ complexes **4a**−**d** was accomplished by precomplexing the pybox ligand with $CuCl_2$ in CH_2Cl_2, followed by halide abstraction with $AgSbF_6$ and filtration[14] to remove the precipitated AgCl (eq 8).[6c,10]



a: R = CMe_3; **b**: R = $CHMe_2$; **c**: R = Ph; **d**: R = Bn

The [Cu((*S*,*S*)-pybox)]$(SbF_6)_2$ complexes **4a**−**d** also catalyze the addition of *tert*-butyl thioacetate trimethylsilylketene acetal to (benzyloxy)acetaldehyde (eq 9) with moderate to excellent enantioselectivity (Table 2, entries 1−5, 62−99% ee). The [Cu-(Ph-pybox)]$(SbF_6)_2$ complex (**4c**) was the most selective catalyst, delivering the β-hydroxy ester with excellent enantioselection within 15 min at −78 °C (entry 5, 99% ee). The analogous triflate complex **3c** was also highly enantioselective, but as anticipated, the reaction was slower (entry 4, 96% ee).

Table 2. Effect of Ligand, Counterion and Temperature in the Catalyzed Benzyloxyacetaldehyde Aldol Reaction (eq 9)



entry	R	X	time (T °C)	% ee[a]
1	CMe_3	SbF_6 (**4a**)	12 h (-78)	62
2	$CHMe_2$	SbF_6 (**4b**)	15 min (-78)	85
3	Bn	SbF_6 (**4d**)	15 min (-78)	67
4	Ph	OTf (**3c**)	60 min (-78)	96
5	Ph	SbF_6 (**4c**)	15 min (-78)	99
6	Ph	SbF_6 (**4c**)	-50[b]	87
7	Ph	SbF_6 (**4c**)	-20[b]	82
8	Ph	SbF_6 (**4c**)	0[b]	78

[a]Enantiomeric excess determined by HPLC using a Chiralcel OD-H column. Absolute configuration determined by comparison of the optical rotation to literature values. [b]Time for complete reaction was not determined in temperature profile study.

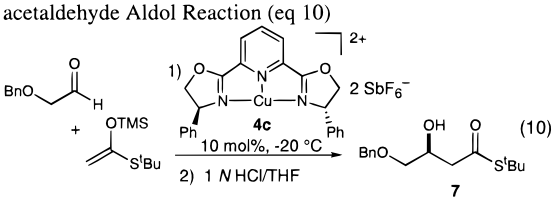
Reaction Optimization. Due to the superior enantioselectivity exhibited by the [Cu((*S*,*S*)-Ph-pybox)]$(SbF_6)_2$ complex (**4c**) (Table 2, entry 5), a study was initiated to explore the (benzyloxy)acetaldehyde aldol reaction parameters with this catalyst system. A survey of permissable solvents for this reaction was undertaken. Solutions of catalyst **4c** in the indicated solvents were generated using the standard procedure. This survey (−20 °C, 10 mol % **4c**) revealed that employment of solvents other than CH_2Cl_2 led to either a significant decline in enantioselectivity or no reaction (Table 3). The inferior results obtained in this solvent screen are likely due to the limited solubility of the [Cu((*S*,*S*)-Ph-pybox)]$(SbF_6)_2$ complex (**4c**) in media other than CH_2Cl_2. An examination of the temperature profile of the [Cu(Ph-pybox)]$(SbF_6)_2$-catalyzed aldol reaction

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

(14) Dry Celite, cotton, or a PTFE 0.45-μm filter gave the best results. Complete removal of the AgCl, as characterized by a clear solution, was essential for obtaining high enantioselectivity.

demonstrated that an increase in the reaction temperature is accompanied by a significant decrease in enantioselectivity (Table 2, entries 6−8). As these reactions are highly exothermic, careful temperature control is critical to the maintenance of high selectivity, especially when executing large-scale preparations (vide infra).

Table 3. Effect of Solvent in the Catalyzed Benzyloxyacetaldehyde Aldol Reaction (eq 10)



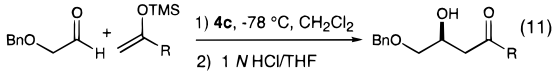
entry	solvent	time	% ee
1	CH_2Cl_2	<15 min	82[a]
2	$ClCH_2CH_2Cl$	10 min	38
3	CH_3CN	12 h	25
4	CH_3NO_2	24 h	ND[b]
5	THF	48 h	NR

[a]At -78 °C, 99% ee was observed. [b]Multiple products observed; enantioselectivity could not be determined.

The effect of transient amounts of water on catalyst performance was also evaluated. Hydration does not appear to significantly impact catalyst reactivity, as substitution of $CuCl_2 \cdot 2H_2O$ for $CuCl_2$ during catalyst preparation afforded [Cu((*S*,*S*)-Ph-pybox)]$(SbF_6)_2$ solutions with similar activity. Furthermore, solutions (0.125 M) of the catalyst **4c** may be stored without loss of catalytic activity for up to 1 week at room temperature, after which time a crystalline solid begins to form. This precipitate has been characterized by X-ray crystallography to be the catalytically inactive 2:1 ligand:copper complex (vide infra). Catalyst loadings as low as 0.5 mol % may be employed in the aldol reaction (eq 9) using this standard [Cu((*S*,*S*)-Ph-pybox)]$(SbF_6)_2$ solution ($[BnOCH_2CHO]_0 = 2.5$ M). Further experiments demonstrated that the implementation of low catalyst loadings is feasible with other substrates as well, the acetate-derived nucleophiles being the most tolerant (vide infra).

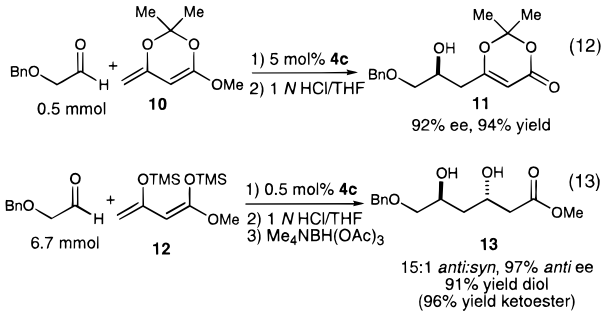
Reaction Scope: [Cu((*S*,*S*)-Ph-pybox)](SbF$_6$)$_2$ (4c). The scope of the nucleophilic component in the (benzyloxy)-acetaldehyde aldol reaction with the catalyst **4c** was initially investigated (Table 4). The silylketene acetals derived from *tert*-butyl thioacetate, ethyl thioacetate, and ethyl acetate reacted with (benzyloxy)acetaldehyde in the presence of 0.5 mol % catalyst to afford the respective β-hydroxy esters with excellent enantioselectivity (entries 1−3, 98−99% ee). In a related series of reactions, acetoacetate-derived enol derivatives were also evaluated (eqs 12 and 13). The dioxolinone derivative **10**[15] underwent facile reaction with (benzyloxy)acetaldehyde, in the presence of 5 mol % **4c**, to provide the corresponding adduct **11** in 92% ee and 94% yield (eq 12).[16] Low catalyst loadings (0.5 mol %) could be employed with the more reactive Chan's diene **12**[17] as the nucleophile, to afford, after reduction with $Me_4NBH(OAc)_3$,[18] the anti diol **13** (15:1 anti:syn) in 97% ee (eq 13).

Table 4. Catalyzed Benzyloxyacetaldehyde Aldol Reaction with Representative Acetate Silylketene Acetals (eq 12)[a]

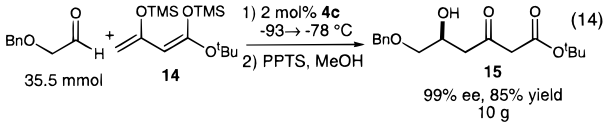


entry	R	catalyst loading	time, h	% ee[b]	% yield
1	S^{t}Bu	0.5 mol%	12-24	99	99
2	SEt	0.5 mol%	12-24	98	95
3	OEt	0.5 mol%	12	98	99[c]

[a]All reactions were 0.2 M in substrate. [b]Enantiomeric excess determined by HPLC using a Chiralcel OD-H column. Absolute configuration determined by independent synthesis (see experimental). [c]The silyl ether was cleaved with TBAF/THF to prevent retroaldol reaction.



In ongoing efforts to exploit the utility of these acetoacetate nucleophiles, the investigation of preparative scale versions of these reactions was undertaken. These studies revealed that the reactions employing the dioxolinone nucleophile (eq 12, 55 mmol) and Chan's diene (eq 13, 40 mmol) were both problematic when conducted on a large scale (80−90% ee, 50−60% yield). However, subsequent optimization studies on the related reaction between (benzyloxy)acetaldehyde and 1,3-bis-(trimethylsiloxy)-1-*tert*-butoxybuta-1,3-diene (**14**)[19] catalyzed by [Cu(Ph-pybox)]$(SbF_6)_2$ (**4c**) established that preparative scale (35.5 mmol) reactions could be performed to deliver the corresponding product (as a mixture of keto−enol tautomers) with high selectivity under slightly modified reaction conditions (eq 14). Due to the exothermic nature of this Cu(II)-mediated



aldol reaction, the optimal procedure required the slow addition of (benzyloxy)acetaldehyde to a −90 °C solution of the catalyst (2 mol %, 0.011 M) and diene (i.e., inverse addition). Desilylation under nonaqueous[20] conditions (PPTS/MeOH) followed by flash chromatography reproducibly afforded good yields of the desired product (**15**)[21] with excellent enantiomeric excess (eq 14, 99% ee, 85% yield). The major competing reaction under these Lewis acidic conditions is the trimerization of (benzyloxy)acetaldehyde, which can be kept under 15% using these conditions. The Ph-pybox ligand routinely recovered during chromatography (ca. 65%) was subsequently recrystallized (EtOAc) for reuse in these Cu(II) catalyzed aldol reactions.

Diastereoselective anti[18] and syn reductions of **15** (eqs 15, 16) permit the efficient production of the synthetically valuable

(15) Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Chem. Pharm. Bull.* **1994**, *42*, 839−845.

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

(17) Brownbridge, P.; Chan, T. H.; Brook, M. A.; Kang, G. J. *Can. J. Chem.* **1983**, *61*, 688−693.

(18) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988,** *110*, 3560−3578.

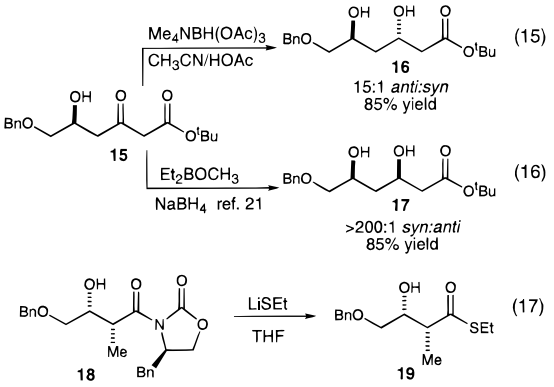
(19) (a) Molander, G. A.; Cameron, K. O. *J. Am. Chem. Soc.* **1993**, *115*, 5, 830−846. (b) This diene was utilized to minimize overreduction to the triol which was observed during the syn reduction of the corresponding methyl ester.

(20) The product is slightly soluble in water.

(21) Beck, G.; Jendralla, H.; Kesseler, K. *Synthesis* **1995**, 1014−1018.

polyacetate building blocks **16** and **17**.[22] Notably, a minor modification of the conditions developed by Beck et al.[21] (see Experimental Section) afforded the syn adduct with excellent diastereoselectivity (>200:1 syn:anti).

Catalyzed Mukaiyama aldol processes are not generally highly diastereoselective, and reactions employing propionate nucleophiles frequently suffer from either low diastereoselectivity or poor reactivity. In contrast, the [Cu((*S*,*S*)-Ph-pybox)]$(SbF_6)_2$ (**4c**)-catalyzed aldol reaction with these nucleophiles affords the substituted adducts with high selectivity (Table 5). For example, the (*Z*) silylketene acetal of ethyl thiopropionate provided the syn aldol adduct in excellent diastereo- and enantioselectivity (97:3 syn:anti, syn 97% ee, Table 5, entry 1). In contrast, the corresponding (*E*) propionate silylketene acetal proved to be an inferior substrate, requiring higher reaction temperature and giving lower conversion and selectivity (86:14 syn:anti, syn 85% ee, entry 2). The absolute and realtive stereochemistries were confirmed by conversion of the known aldol product **18**[23] to the syn adduct **19**, which exhibited the expected opposite sign of optical rotation (eq 17).



(15) (16) (17)

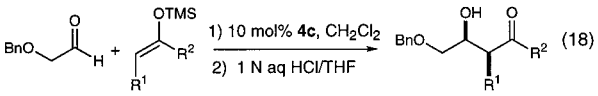
The exact nature of the silyl component of the silylketene acetal was not critical, as the (*Z*)-propionate-derived *tert*-butyldimethylsilylketene acetal afforded similar selectivity (94:6 syn:anti, syn 96% ee, entry 3) in comparison to the trimethylsilyl analogue (97:3 syn:anti, syn 97% ee, entry 1). Thus, additional protecting group steps are obviated as this manipulation can be merged with the copper-catalyzed Mukaiyama aldol reaction to provide β-hydroxy carbonyl products with an intact, synthetically useful silyl ether protecting group. The use of silylketene acetals with larger alkyl substituents is also permitted, as evidenced by the production of the isobutyl-substituted adduct (eq 17, R^1 = ^{i}Bu) with high diastereo- and enantioselectivity and good yield (Table 5, entry 4, 95:5 syn:anti, 95% ee, 85%).

While *tert*-butyl thioester- or ethyl ester-derived silylketene acetals could also be employed, the results were not as favorable as those obtained with ethyl thioester-derived nucleophiles (Table 5, entry 1 vs entries 5−7). Regardless of the precise nature of the ester substituent, the best selectivity and reactivity for the substituted silylketene acetals were obtained when the alkyl and OTMS moieties were disposed in an anti orientation about the silylketene acetal double bond. This geometric requirement was also evident in the analogous reaction of the butyrolactone silylketene acetal, which afforded a highly selective syn aldol reaction with good control at both stereogenic centers (eq 19).

(22) We have also carried out the same sequence of reactions (eqs 14−16) employing (4-methoxybenzyloxy)acetaldehyde with similar yields and selectivities.

(23) Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 3448−3467.

Table 5. Catalyzed Benzyloxyacetaldehyde Aldol Reaction with Representative Substituted Silylketene Acetals (eq 18)

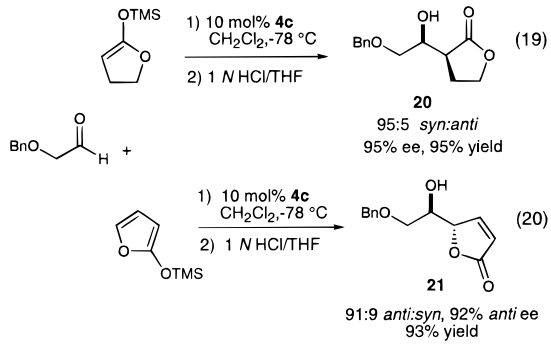


(18)

entry	R^1	R^2	(Z):(E)	time/T (°C)	*syn:anti*[a]	% ee[a,b]	% yield
1	Me	SEt	95:5	4 h /-78	97:3	97	90
2	Me	SEt	1:99	1 d/-50	86:14	85	48
3[c]	Me	SEt	94:6	5 h/-65	94:6	96	70
4	^{i}Bu	SEt	90:10	2 d/-50	95:5[d]	95[d]	85
5	Me	S^{t}Bu	95:5	1 d/-50	85:15	99	86
6	Me	S^{t}Bu	4:96	1 d/-50	85:15	97	14
7	Me	OEt[e]	15:85	15 min/-95	84:16	87	60[f]
8	Ph	OEt[e]	30:70	25 min/-78	50:50[d]	9[d]	ND[g]
9	OBn	SEt	90:10	1 d/-50	74:26	76	21[f]
10	OBn	SEt	25:75	2 d/-20	86:14	63	11[h]

[a]Product ratios determined by HPLC using a Chiralcel OD-H or AD column. Absolute and relative configuration determined by independent synthesis (see Experimental). [b]Enantiomeric excess of the major product diastereomer. [c]A *tert*-butyldimethylsilyl ether was employed. The silyl ether could be isolated in 68% yield along with ~10% alcohol. HF in MeCN was required to remove the silyl ether. [d]Configuration assigned by analogy. [e]Note that the (*E*) and (*Z*) designators change for esters relative to thioesters. [f]≥90% conversion was observed by ^{1}H-NMR, but considerable decomposition occurred during silyl ether removal and product isolation. [g]Complete conversion observed by TLC. [h]Approximately 50% conversion by TLC.

Attempts to employ non-alkyl-substituted silylketene acetals as the nucleophilic component (eq 18, $R^1 \neq$ alkyl), such as phenylacetate and benzyloxythioacetate, were unsuccessful (Table 5, entries 8−10). On the other hand, 2-(trimethylsilyloxy)furan[24] underwent facile reaction with (benzyloxy)acetaldehyde in the presence of the [Cu(Ph-pybox)]$(SbF_6)_2$ catalyst (**4c**) to afford the anti aldol adduct **21** in high yield with excellent diastereo- and enantioselectivity (eq 20).[25] The densely functionalized product of this reaction is a versatile synthon for natural product synthesis and also may be elaborated to unnatural hexose derivatives.[24] Although the inherent stereoconvergency of this Cu(II)-catalyzed process permits access primarily to the syn aldol adducts, anti diastereoselectivity can be accessed through the use of the Sn(II)-box-catalyzed aldol reactions of glyoxylate esters.[26] Thus, the copper and tin catalysts together provide a powerful entry into a diverse array of substituted aldol products.



(19) (20)

While ester silylketene acetals were successfully utilized in this reaction, thioester silylketene acetals offer several advan-

(24) Casiraghi, G.; Rassu, G. *Synthesis* **1995**, 607−626.

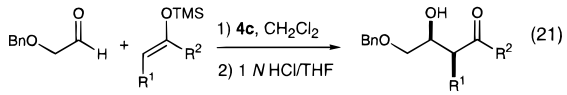
(25) Anti diastereoselectivity was also observed with this nucleophile in the Cu(II) catalyzed pyruvate aldol reaction; see the following article in this issue Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686−699. The absolute and relative stereochemistry of this product were secured by X-ray analysis of the corresponding menthyl carbonate (see Supporting Information).

(26) Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859−10860.

tages. These latent nucleophiles are easily prepared and more stable than the corresponding ester derivatives, which undergo rapid hydrolysis.[27] In addition, the thioester moiety in the resultant adducts can be readily converted to an acid, amide, or ester using either a silver-based reagent[28] or a bromination/displacement procedure.[29] Alternatively, the Fukuyama reduction procedure (Pd/C, Et_3SiH) can be implemented to reduce thioesters to aldehydes.[30]

The less reactive ketone enolsilane nucleophiles may also be utilized in the catalyzed additions to (benzyloxy)acetaldehyde (Table 6). The reactions of 2-(trimethylsilyloxy)propene and 1-phenyl-1-(trimethylsilyloxy)ethylene with (benzyloxy)acetaldehyde proceeded poorly at 10 mol % catalyst loading (≤56% ee); however, high enantioselectivity and yields were realized upon employment of stoichiometric quantities of the catalyst (≥94% ee; Table 6, entries 1 and 2).

Table 6. Catalyzed Benzyloxyacetaldehyde Aldol Reaction with Representative Enolsilanes (eq 21)[a]



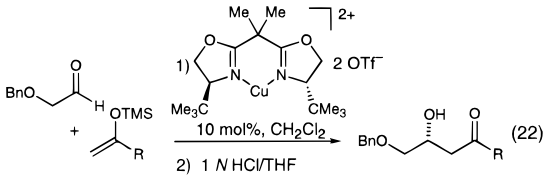
entry	R^1	R^2	(*E*):(*Z*)	catalyst loading	time (T °C)	*syn*:*anti*[b]	% ee[b,c]	% yield
1	H	Me	--	100 mol%	1 d (-78)	--	98	96
2	H	Ph	--	100 mol%	1 d (-78)	--	94	80
3	Me	^{i}Pr	90:10	10 mol%	2 d (-20)	95:5	90	90
4	Me	^{i}Pr	10:90	10 mol%	2 d (-20)	38:62	28[d]	10
5	-$(CH_2)_3$-		--	10 mol%	14 h (-78)	97:3	96	90

[a] All reactions were 0.2 M in substrate. [b] Product ratios determined by chiral HPLC. Absolute and relative configuration determined by independent synthesis (see Experimental). [c] Enantiomeric excess of the major product diasteromer. [d] 35% *syn* ee observed.

The more nucleophilic[31] substituted enolsilanes were found to be superior substrates in these reactions as compared to their unsubstituted counterparts (Table 6, entries 3−5). For example, the reaction of the (*E*) enolsilane of 2-methyl-3-pentanone proceeded to complete conversion in the presence of 10 mol % of the copper catalyst **4c** to afford the corresponding adduct with 95:5 syn:anti selectivity and 90% ee. As anticipated (vide supra), the analogous (*Z*) enolsilane was both less reactive and less enantioselective (entry 3 vs 4). The successful implementation of 1-(trimethylsilyloxy)cyclopentene demonstrates that cyclic enolsilanes are also excellent nucleophiles in the (benzyloxy)acetaldehyde aldol reaction (entry 5, 97:3 syn:anti, 96% ee).

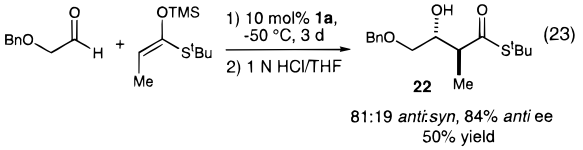
Reaction Scope: [Cu((*S*,*S*)-*tert*-Bu-box)](OTf)$_2$ (1a). Examination of the scope of the nucleophilic component in the additions to (benzyloxy)acetaldehyde catalyzed by **1a** was next undertaken (Table 7). The thioester silylketene acetal (entry 1, 91% ee) afforded significantly higher selectivity than to the ester derivative (entry 2, 50% ee). Additionally, the use of enolsilane nucleophiles resulted in the formation of the aldol adducts with diminished selectivity (entries 3 and 4). These results clearly indicate that the [Cu((*S*,*S*)-Ph-pybox)]$(SbF_6)_2$ complex (**4c**) is the preferred catalyst for acetate aldol reactions with (benzyloxy)acetaldehyde.

Table 7. Catalyzed Benzyloxyacetaldehyde Aldol Reaction with Representative Enolsilanes (eq 22)



entry	R	time (T °C)	% ee
1	S^{t}Bu	1 h/-78	91
2	OEt	15 min/-78	50
3	Me	6 h/-20	38
4	Ph	1 d/-20	51

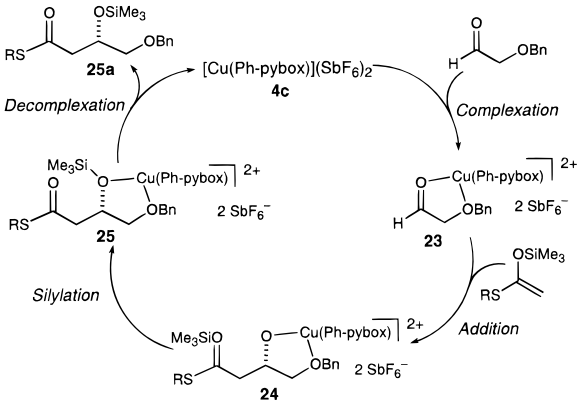
Investigation into the use of propionate nucleophiles with the [Cu(*tert*-Bu-box)](OTf)$_2$ catalyst system **1a** revealed that the addition of *tert*-butyl thiopropionate trimethylsilylketene acetal to (benzyloxy)acetaldehyde proceeded with anti diastereoselectivity (eq 23, 81:19 anti:syn, 84% anti ee).[4c] Although the yield



for this reaction (50%) is not preparatively useful, it serves to illustrate that diastereoselection is not simply inherent to the nature of the process but is a consequence of an array of factors, among the most important of which is the geometry of the substrate−catalyst complex (vide infra). Further studies are required in order to define the origin of this reversal in selectivity.

Reaction Mechanism. The proposed catalytic cycle for the Cu(II)-catalyzed aldol reaction is outlined in Scheme 4. Coordination of (benzyloxy)acetaldehyde to the Cu(II) center produces the substrate−catalyst complex **23**, which undergoes nucleophilic addition to afford the copper aldolate **24**. Silylation to form **25** and subsequent decomplexation yields the product **25a** and concomitantly regenerates the [Cu((*S*,*S*)-Ph-pybox)]$(SbF_6)_2$ catalyst (**4c**).

Scheme 4



(27) These thioester silylketene acetals can be stored at −20 °C for extended periods of time. For their preparation, see the following. (a) Silylketene acetals of ethyl and *tert*-butyl thioacetate: Kobayashi, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 297−300. (b) (*E*)- and (*Z*)-silylketene acetals of ethyl and *tert*-butyl thiopropionate: Gennari, C.; Beretta, M. G.; Bernardi, A.; Moro, G.; Solastico, C.; Todeschini, R. *Tetrahedron* **1986**, *42*, 893−909.

(28) Booth, P. M.; Fox, C. M. J.; Ley, S. V. *Tetrahedron Lett.* **1983**, *46*, 5143−5146.

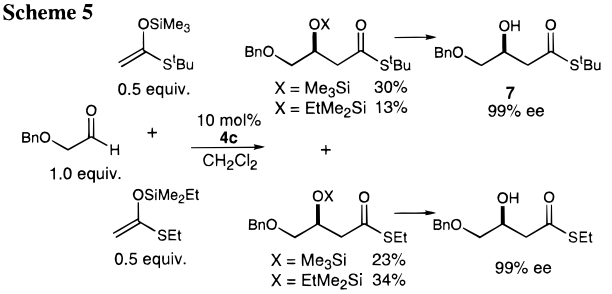
(29) (a) Using NBS: Minato, H.; Kodama, H.; Miura, T.; Kobayashi, M. *Chem. Lett.* **1977**, 413−416. (b) Using Br_2: Minato, H.; Takeda, K.; Miura, T.; Kobayashi, M. *Chem. Lett.* **1977**, 1095−1098.

(30) Fukuyama T.; Lin S.-C.; Li L. *J. Am. Chem. Soc.* **1990**, *112*, 7050−7051.

(31) Bufeindt, J.; Patz, M.; Müller, M; Mayr, H. *J. Am. Chem. Soc.* **1998**, *120*, 3629−3634.

Silyl Crossover Experiments. It is evident that silicon transfer from the initially formed catalyst−Nu−RCHO complex **24** may proceed via an intramolecular or intermolecular process (Scheme 4, **24** → **25**). It has been reported that intermolecular silyl transfer, for example either to counterion ($SbF6^-$ or OTf^-) or to unreacted aldehyde, may trigger an *achiral* catalyzed process that may compete with the enantioselective variant.[32] The details associated with silicon transfer were investigated in the present system by employing a mixture of two different silylketene acetals of comparable reactivities (Scheme 5).[4c]

Scheme 5



Treatment of 0.5 equiv of each of the depicted silylketene acetals with 1.0 equiv of (benzyloxy)acetaldehyde and 10 mol % of [Cu(Ph-pybox)]$(SbF_6)_2$ (**4c**) afforded significant quantities of the four possible products, as detected by GC/MS analysis. Deprotection of the silyl ethers and chiral HPLC analysis of the derived alcohols indicated that both aldol adducts were essentially enantiomerically pure (99% ee). Although there is clearly a large intermolecular silyl-transfer component in the reaction, the transient silyl species[33] apparently does not compete effectively at −78 °C with the *biscationic* copper catalyst in this aldol reaction. Control experiments demonstrated that neither the silylketene acetals nor the silyl ether products are subject to silyl exchange initiated by the catalyst, indicating that silyl crossover occurs during the course of the reaction.

Nonlinear Effects. Nonlinear effects (NLE) can provide useful insight into both the behavior of enantioselective catalyst systems and the mechanisms of the processes they mediate.[34,35] Consequently, experiments were performed to determine if NLE were operative in the Cu(II) pybox-catalyzed aldol reaction under investigation. Indeed, when the aldol reaction was conducted with the catalyst [Cu(Ph-pybox)]$(SbF_6)_2$ (10 mol %) prepared according to the general procedure with ligand of reduced enantiomeric excess (eq 24), a strong positive nonlinear effect was observed (Figure 1). For example, employment of a catalyst of 25% ee afforded the aldol adduct in 74% ee.

To rationalize this significant NLE, we propose that catalyst disproportionation is occurring under the conditions for catalyst preparation (eq 26, CH_2Cl_2, 20 °C, 4 h). The formation of a stable [Cu((*S*,*S*)-Ph-pybox)((*R*,*R*)-Ph-pybox)]$(SbF_6)_2$ 2:1 ligand:metal complex (**26**) is postulated, serving as a catalytically inactive reservoir for the minor (*R*,*R*)-Ph-pybox ligand and consequently enriching the enantiomeric excess of the remaining

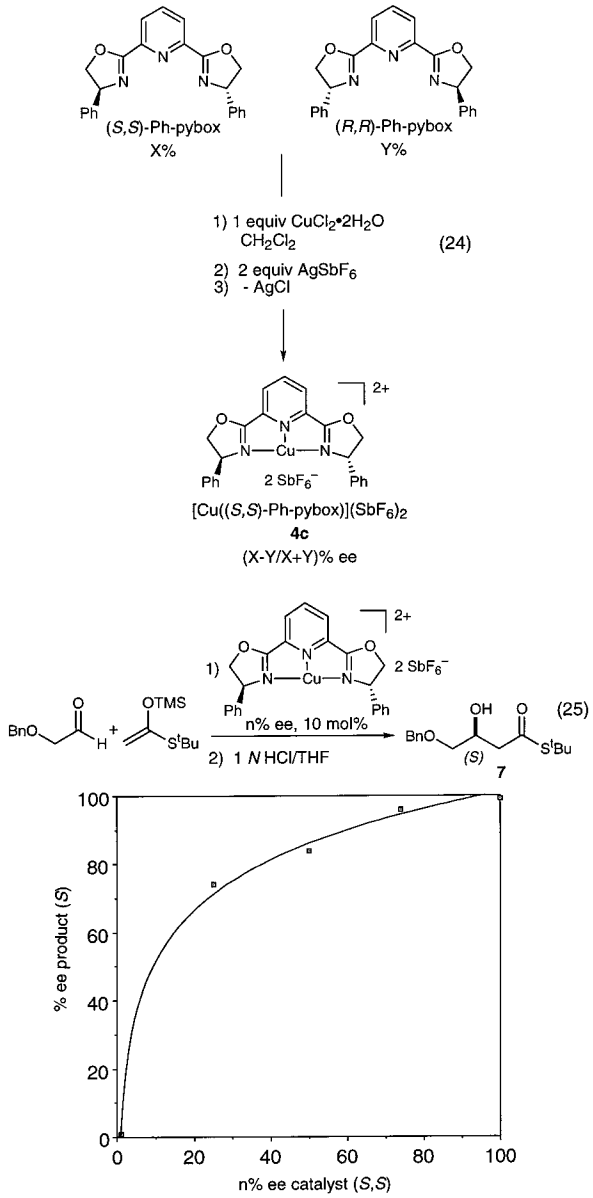
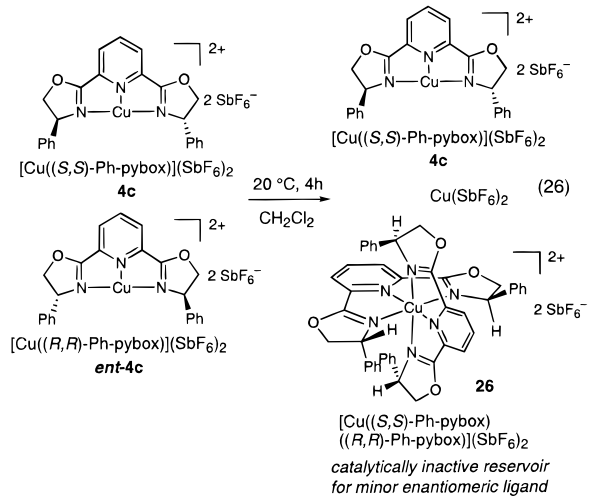


Figure 1. Nonlinear effect in the benzyloxyacetaldehyde aldol reaction with the [Cu(Ph-pybox)]$(SbF_6)_2$ catalyst.

[Cu((*S*,*S*)-Ph-pybox)]$(SbF_6)_2$ catalyst (**4c**) (eq 26).[36] As these reactions were conducted using a 1:1 ratio of ligand:Cu, stoichiometry necessitates the production of an unligated copper



(32) (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.

(33) Potential silylating sources include **24** and Me_3SiSbF_6: Olah, G. A.; Heiliger, L.; Li, X.−Ya; Prakash, G. K. S. *J. Am. Chem. Soc.* **1990**, *112*, 5991−5995.

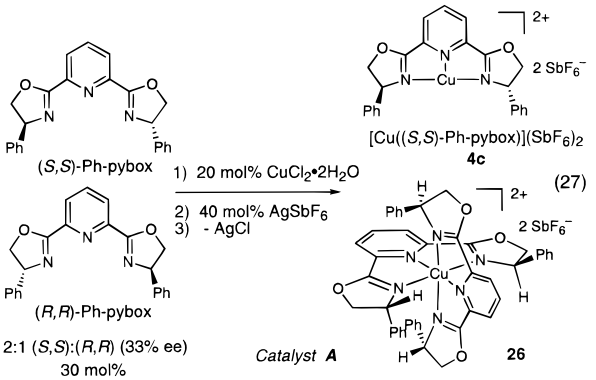
(34) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2923−2959 and references therein.

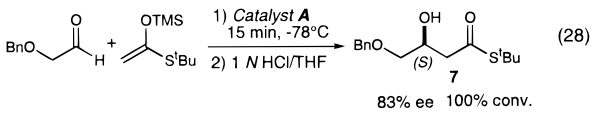
(35) A very informative study on NLE in the DBFOX/Ph·$Ni(ClO_4)_2$ catalyst system appeared during the preparation of this manuscript: Kanemasa, S.; Oderaotoshi, Y.; Sakaguchi, S.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Am. Chem. Soc.* **1998,** *120*, 3074−3088.

species. Plausible fates of the released Cu(II) include the formation of $Cu(SbF_6)_2$[37] or a non-Lewis acidic species such as CuO or $Cu(OH)_2$.

Several control experiments were performed to provide support for the NLE proposal. Independent generation of the 2:1 ligand:copper complex using our standard catalyst preparation procedure afforded a material that was nearly completely insoluble in the reaction solvent.[38] Subjection of this solution to the (benzyloxy)acetaldehyde aldol reaction revealed that the 2:1 ligand:copper complex was not a catalytically competent species (−78 °C, 2 d, 9% yield vs **4c**, −78 °C, 15 min, 99% yield). This result, buttressed by the fact that as little as 0.5 mol % of the catalyst **4c** is capable of effecting the reaction within 24 h at −78 °C (Table 4), also serves to demonstrate that once the 2:1 ligand:metal complex is formed, it is not in an appreciable equilibrium with catalyst **4c**. Furthermore, the addition of 1 equiv of (*R*,*R*)-Ph-pybox ligand to a stock solution of [Cu((*S*,*S*)-Ph-pybox)]$(SbF_6)_2$ (**4c**) caused the immediate (≤30 s) precipitation of a pale blue amorphous material (presumably the 2:1 complex) and a clear colorless solution,[39] indicating that the formation of the insoluble 2:1 (*S*,*S*)−(*R*,*R*) ligand metal-complex **6** is a facile process at room temperature.

To delineate the course of ligand exchange and the relative stabilities of the (*S*,*S*)−(*R*,*R*) and (*S*,*S*)−(*S*,*S*) 2:1 ligand:metal complexes, a catalyst preparation was undertaken using excess ligand relative to copper (eq 27). The use of 30 mol % of 2:1





(*S*,*S*):(*R*,*R*) ligand (33% ee) and 20 mol % $Cu(SbF_6)_2$ (i.e., 20 mol % $CuCl_2$ and 40 mol % $AgSbF_6$) should, ideally, produce 10 mol % of the [Cu((*S*,*S*)-Ph-pybox)((*R*,*R*)-Ph-pybox)]$(SbF_6)_2$ complex (**26**) and 10 mol % of enantiomerically enriched [Cu((*S*,*S*)-Ph-pybox)]$(SbF_6)_2$ (**4c**) (catalyst **A**). Employment of this catalyst solution[40] in the reaction of (benzyloxy)acetaldehyde with *tert*-butyl thioacetate silylketene acetal provided the aldol product in 83% ee within 15 min at −78 °C (eq 28). Although the enantioselectivity of this reaction did not approach the selectivity obtained in the reaction catalyzed by enantiomerically pure **4c** (99% ee, 15 min, −78 °C), it did surpass the enantioselectivity observed in the NLE experiment (e.g., 50% ee ligand → 84% ee product, Figure 1). Thus, this experiment illustrates both that enrichment of the ligand is being achieved through the formation of the [Cu((*S*,*S*)-Ph-pybox)((*R*,*R*)-Ph-pybox)]$(SbF_6)_2$ complex (**26**) and that this species is favored relative to the (*S*,*S*)−(*S*,*S*) 2:1 ligand:metal complex.

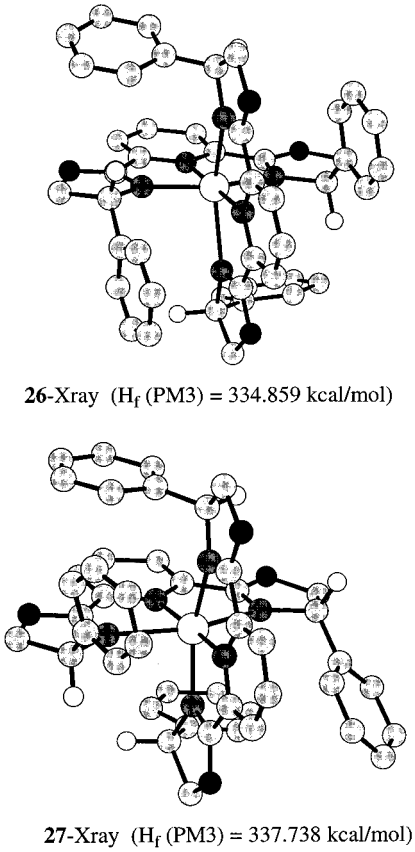


Figure 2. Crystal structures of the 2:1 Ph-pybox:copper complexes [Cu((*S*,*S*)-Ph-pybox)((*R*,*R*)-Ph-pybox)]$(SbF_6)_2$ (**26**-X-ray) and [Cu((*S*,*S*)-Ph-pybox)$_2$]$(SbF_6)_2$ (**27**-X-ray). Counterions have been omitted for clarity.

Ultimate corroboration for the formation of a catalytically inactive 2:1 ligand:metal complex was obtained through the X-ray crystal structural determination of both the [Cu((*S*,*S*)-Ph-pybox)((*R*,*R*)-Ph-pybox)]$(SbF_6)_2$ (**26**) and [Cu((*S*,*S*)-Ph-pybox)$_2$]$(SbF_6)_2$ (**27**) complexes (Figure 2). By inspection, the (*S*,*S*)−(*R*,*R*) complex **26** appears favored relative to (*S*,*S*)−(*S*,*S*) complex **27**, as the ligand phenyl groups project unobstructed into each of the four quadrants. In comparison, in **27** the phenyl groups of the ligands protrude into the same two quadrants. Semiempirical calculations (PM3) qualitatively validated this analysis, as the heat of formation of the (*S*,*S*)−(*R*,*R*) complex **26** was found to be 2.9 kcal/mol lower in energy than that of the (*S*,*S*)−(*S*,*S*) complex **27**.

Catalyst Characterization and Stereochemical Models: [Cu(Ph-pybox)]$(SbF_6)_2$. The proposed requirement for chelation in the [Cu((*S*,*S*)-Ph-pybox)]$(SbF_6)_2$ (**4c**)-mediated (benzyloxy)-

(36) We have previously observed positive NLE in the Sm(III)-catalzyed Meerwein−Pondorf−Verley reduction and the Cu(II)−catalyzed Diels−Alder reaction: Evans, D. A.; Nelson, S. G.; Gagné, M.; Muci, A. R. *J. Am. Chem. Soc.* **1993,** *115*, 9800−9801.

(37) To avoid achiral catalysis, the formation of $Cu(SbF_6)_2$ would apparently necessitate that this complex be either insoluble in CH_2Cl_2 or a noncompetitive catalyst. While the preparation of $Cu(SbF_6)_2$ as a white solid has been reported, to our knowledge its solubility in common organic solvents has not been studied: (a) Cader, M. S. R.; Aubke, F. *Can. J. Chem.* **1989**, *67*, 1700−1701. (b) Gantar, D.; Leban, I.; Frlec, B.; Holloway, J. H. *J. Chem. Soc., Dalton Trans.* **1987**, 2379−2382.

(38) A dark blue precipitate (presumably the 2:1 complex) and a very pale blue solution were observed.

(39) Solutions of **4c** are blue and free of precipitate; thus, it appears that colorless solutions contain very little or no copper species.

(40) A pale blue precipitate (presumably the 2:1 complex) and a blue solution were observed (eq 28).

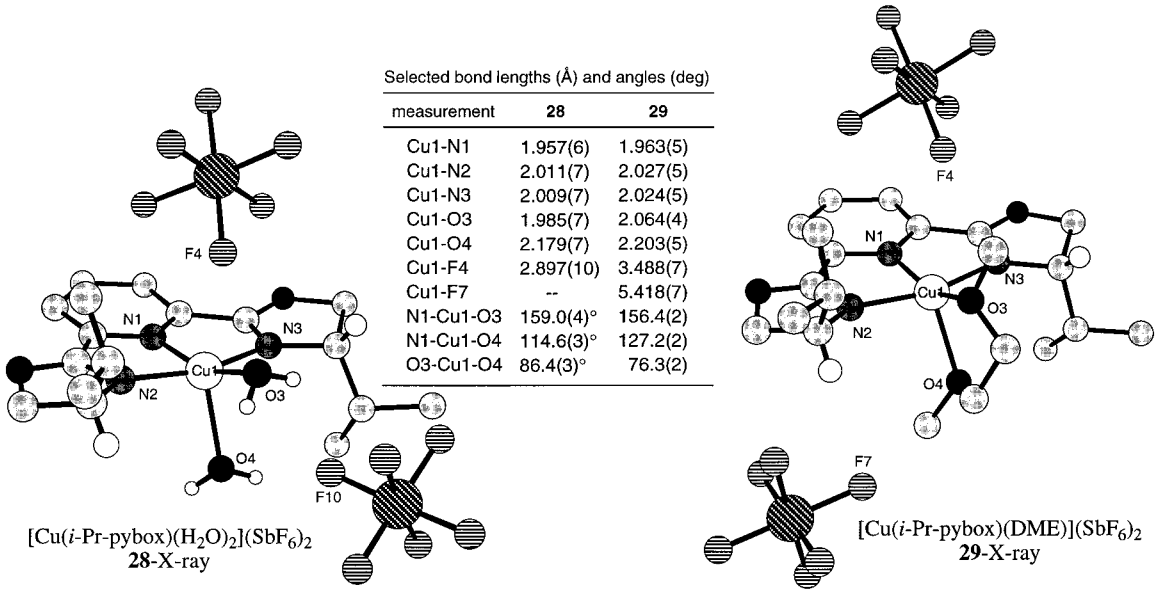


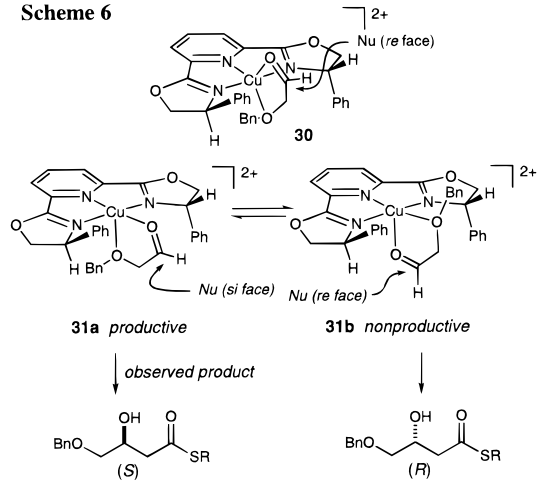
Figure 3. Crystallographic structures of the [Cu(*i*-Pr-pybox)(L)$_n$](SbF$_6$)$_2$ complexes **39** and **40** along with selected bond lengths and angles.

acetaldehyde aldol reaction requires the intermediacy of a five-coordinate Cu(II) catalyst−substrate complex.[41,42] Several five-coordinate [Cu(pybox)](SbF$_6$)$_2$ complexes were synthesized with the intent of obtaining crystal structures that might elucidate the basic coordination geometry (i.e., trigonal bipyramidal or square pyramidal)[43] of these complexes, thus providing a basis upon which to construct a stereochemical model of the catalyst−substrate complex. Due to the highly crystalline nature of the bis(hydrate), [Cu(*i*-Pr-pybox)(H$_2$O)$_2$](SbF$_6$)$_2$ (**28**, Figure 3) was selected as the initial substrate from which to extrapolate geometrical information on pentacoordinate Cu(II) complexes. Efforts were also directed toward obtaining crystals of chelated pentacoordinated [Cu(pybox)]$^{2+}$ complexes to model this reaction, in which the catalyst−substrate complex is similarly organized. In this context, we also obtained an X-ray structure of the analogous dimethoxyethane (DME) complex **29** (Figure 3). Both the bis(hydrate) and the DME complexes **28** and **29** adopt a square pyramidal geometry, with the SbF$_6$ counterions fully dissociated from the metal center (Figure 3). A useful measure of distortion from the ideal square pyramidal geometry is the N1$_{(pyridyl)}$−Cu−O3$_{(equat)}$ bond angle, which by definition is 180° for an undistorted complex. For the DME complex **29**, this measure of distortion (N1−Cu1−O3 = 156.4°) is somewhat greater than the corresponding measurement in the bis(hydrate) complex **28** (N1−Cu1−O3 = 159.0°).

As a consequence of the electronic configuration of the Cu(II) center (d^9) and accompanying Jahn−Teller distortion, the square pyramidal geometry affords a strong coordinating site in the ligand plane, with a weaker coordination site in the axial position.[42] In accord with this expectation, the more tightly bound oxygen heteroatoms in **28** and **29** are found in the equatorial plane (**28**, Cu−OR$_2$ = 1.985 Å; **29**, Cu−OR$_2$ = 2.064 Å), with the more weakly coordinated oxygen ligand positioned in the apical site of the complexes (**28**, Cu−OR$_2$ = 2.179 Å; **29**, Cu−OR$_2$ = 2.203 Å). From these data, it is reasonable to conclude that the Cu−O bond lengths in **29** provide a direct measure of the inherent Lewis acidity of the two nonequivalent catalyst binding sites.

Based upon the preceding structural data, the trigonal bipyramidal complex **30** was considered unlikely; furthermore, this structure predicts the incorrect stereochemical outcome for the (benzyloxy)acetaldehyde aldol reaction (Scheme 6). For the

Scheme 6



square pyramidal copper geometry, two diastereomeric catalyst−substrate complexes **31a** and **31b** must be considered in the analysis of the impact of catalyst structure on reaction stereochemistry. As documented in the [Cu(pybox)]$^{2+}$ system by the X-ray crystal structures **28** and **29**, the square pyramidal geometry affords a strong coordinating site in the ligand plane, with a weaker coordination site in the axial position. As a consequence, for maximal carbonyl activation, aldehyde coordination is postulated to occur in the equatorial position, as illustrated in complex **31a**. Accordingly, the catalyst−substrate complex **31a**, successfully predicts the stereochemical outcome of the (benzyloxy)acetaldehyde aldol reaction, and the diastereomeric square pyramidal complex **31b** predicts the wrong absolute stereochemistry. The high enantioselectivity observed

(41) The weakly coordinating SbF$_6$ counterions are presumed to not associate directly with the Cu(II) center. Considerable structural data support this assertion (vide infra).

(42) (a) For a discussion of five-coordinate Cu(II) complexes, see: Hathaway, B. J. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Ed.; Pergamon Press: New York, 1987; Vol. 5, Chapter 53. (b) Cambridge Structural Database survey: 51 square pyramidal structures; 9 trigonal bipyramidal structures (http://sulfur.scs.uiuc.edu/gifs/cuii.htm).

(43) The energy difference between trigonal bipyramidal and square pyramidal geometries has been calculated to be low; see: (a) Wilcox, D. E.; Porras, A. G.; Hwang, Y. T.; Lerch, K.; Winkler, M. E.; Solomon, E. I. *J. Am. Chem. Soc.* **1985**, *107*, 4015−4027. (b) Solomon, E. I. *Comments Inorg. Chem.* **1984**, *3*, 227−320.

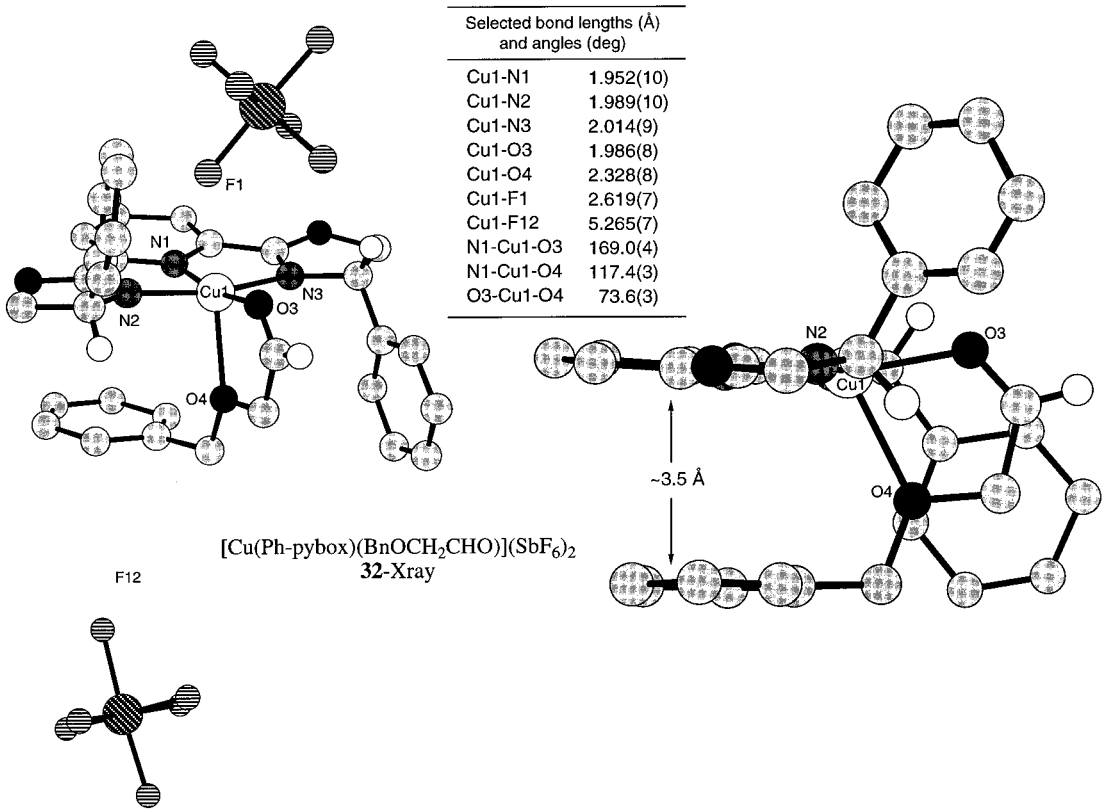
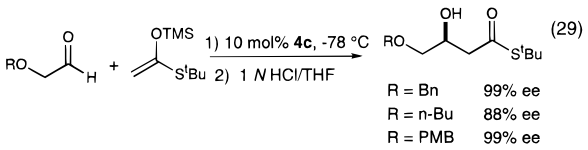


Figure 4. Two perspectives of the X-ray structure of the [Cu(Ph-pybox)(BnOCH$_2$CHO)](SbF$_6$)$_2$ complex **41** along with selected bond lengths and angles.

in these reactions (≥95% ee) provides strong support for the assertion that only one of the two complexes, i.e., **31a**, is catalytically competent.

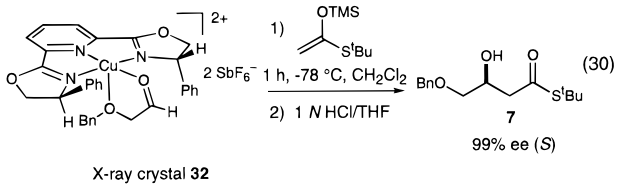
Ultimately, we were successful in obtaining deep blue crystals of the catalyst−substrate [Cu((*S*,*S*)-Ph-pybox)(BnOCH$_2$CHO)](SbF$_6$)$_2$ complex (**32**). The X-ray structure reveals that the copper geometry is square pyramidal, with the carbonyl oxygen coordinated to the equatorial site in the ligand plane and the ether oxygen occupying an apical site (Figure 4). As expected, the carbonyl oxygen occupies the more Lewis acidic site as evidenced by the much shorter aldehyde−Cu bond length (Cu1−O3 = 1.986 Å) relative to the benzyl ether−Cu bond length (Cu1−O4 = 2.328). This complex exhibits a minimal amount of distortion from an ideal square pyramidal geometry, as evidenced by the N1$_{(pyridyl)}$−Cu−O3$_{(equat)}$ bond angle of 169.0°. In direct accord with our prediction, it is evident from this structure that the *re* face of the aldehyde carbonyl is completely shielded by the Ph substituent on the ligand.

Further inspection of the [Cu(Ph-pybox)(BnOCH$_2$CHO)](SbF$_6$)$_2$ X-ray structure (**32**) reveals that the phenyl group of the (benzyloxy)acetaldehyde substrate is oriented under the pyridine ring of the pybox ligand (~3.5 Å) in a parallel fashion (Figure 4). This geometrical arrangement and distance are consistent with a parallel offset face-to-face $\pi-\pi$ interaction between the phenyl and pyridyl moieties.[44] Experiments were designed to counter the possibility that the observed orientation is solely a consequence of crystal packing and of no relevance to the actual solution behavior. Upon substitution of the benzyl group of the substrate with an alkyl group, as in (*n*-butyloxy)-acetaldehyde, a significant reduction in enantioselectivity was observed (eq 29, 99 → 88% ee, $\Delta\Delta G^{\ddagger} \approx 1$ kcal/mol at −78 °C). When the aryl group was reinstalled, as in (4-methoxybenzyloxy)acetaldehyde, the enantioselection was restored to 99% ee (eq 29). These experiments suggest that this $\pi-\pi$ interaction plays an important organizational role in the assembly of the catalyst−substrate complex.[45]



(29)

When the [Cu((*S*,*S*)-Ph-pybox)(BnOCH$_2$CHO)](SbF$_6$)$_2$ crystals (**32**) were redissolved in CH_2Cl_2 and treated with the silylketene acetal derived from *tert*-butyl thioacetate under the usual reaction conditions (eq 30), the aldol adduct was obtained in 99% ee (1 h, −78 °C), the same value as obtained for the catalyzed reaction. This experiment provides strong evidence that the catalyst−aldehyde complex (**32**) isolated and characterized is also the catalytically relevant species in solution.



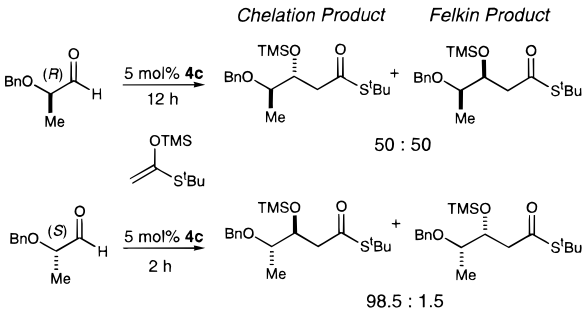
(30)

Evidence for Chelation. The selection of (benzyloxy)-acetaldehyde as the aldol reaction substrate was predicated upon the proposed ability of this aldehyde to engage in bidentate

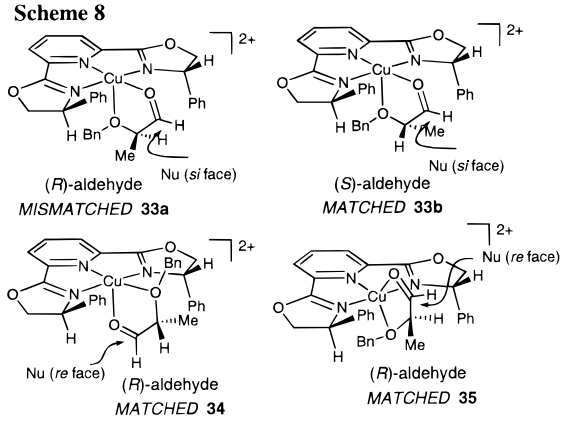
(44) Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525−5534

(45) For examples where $\pi-\pi$ interactions in enantioselective catalyst systems have been characterized by X-ray crystallography, see: (a) Hawkins, J. M.; Loren, S.; Nambu, M. *J. Am. Chem. Soc.* **1994**, *116*, 1657−1660. (b) Quan, R. W.; Li, Z.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 8156−8157.

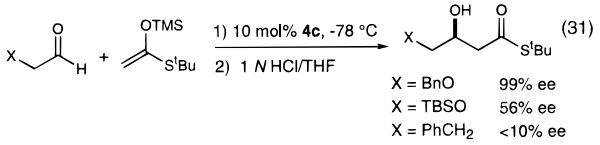
Scheme 7



Scheme 8



coordination to the Cu(II)-center. Support for dynamic substrate chelation was acquired when α-(*tert*-butyldimethylsilyloxy)-acetaldehyde, an aldehyde which is expected to be an ineffective chelator,[46] was implemented in the Cu(II)-catalyzed aldol reaction: the use of this aldehyde led to a less enantioselective process (eq 31, 56% ee) as compared to (benzyloxy)acetaldehyde (99% ee). Furthermore, hydrocinnamaldehyde, a monodentate substrate incapable of chelation, afforded a racemic product when employed in this reaction (eq 31). Based upon these results, catalyst−substrate chelation appears to be an absolute requirement for obtaining high enantioselectivity in this process.



(31)

Double stereodifferentiating experiments with (*R*)- and (*S*)-α-(benzyloxy)propionaldehyde have also been carried out to provide support for the square pyramidal catalyst−substrate model **31a** described in Scheme 6. Gennari and Cozzi have shown that the $SnCl_4$-mediated addition of the silylketene acetal derived from *tert*-butyl thioacetate to α-(benzyloxy)propionaldehyde provides the chelation-controlled adduct with high selectivity (98:2).[47] Reaction of (*R*)-α-(benzyloxy)propionaldehyde catalyzed by [Cu(Ph-pybox)]$(SbF_6)_2$ afforded an unselective, slow reaction (Scheme 7, *mismatched*). This result is consistent with catalyst−substrate square pyramidal coordination, where the substrate (Me) and ligand (Ph) substituents mask *opposite* aldehyde carbonyl enantiofaces (Scheme 8, **33a**). In the *matched* case, (*S*)-α-(benzyloxy)propionaldehyde underwent a rapid reaction, providing a 98.5:1.5 mixture of diastereomers, favoring the chelation-controlled product (Scheme 7). In the square pyramidal complex (Scheme 8, **33b**), the α-methyl substituent of (*S*)-α-(benzyloxy)propionaldehyde reinforces the facial bias imposed by the catalyst.

A corollary to these experiments is that (*R*)-α-(benzyloxy)-propionaldehyde would be anticipated to act as a catalyst inhibitor on the basis of the observation that this enantiomer ideally complements the catalyst by orienting a Me group in the only open quadrant available in complex **33a** (Scheme 8). Indeed, this has been shown to be the case, as demonstrated by the low reactivity of (*R*)-α-(benzyloxy)propionaldehyde. While the manifestation of matched and mismatched reaction partners is consistent with all the models, both the diastereomeric square pyramidal model **34** and the trigonal bipyramidal model **35** would predict the *opposite* matched and mismatched relationships relative to those observed (Scheme 8); moreover, the results of these double stereodifferentiating experiments are in full accord with the proposal that (benzyloxy)acetaldehyde coordinates to the Cu(II) center in a bidentate fashion.

Solution-State Characterization. To establish a correlation between the accumulated solid-state structural data and the solution behavior, the catalyst−substrate species were probed using a combination of electrospray ionization mass spectrometry (ESI) and electron paramagnetic resonance (EPR) spectroscopy. Significantly, the ESI spectrum of [Cu(Ph-pybox)-$(BnOCH_2CHO)](SbF_6)_2$ clearly affirmed the presence of a doubly charged catalyst−substrate complex, [Cu(Ph-pybox)-$(BnOCH_2CHO)]^{2+}$, in solution without any associated counterions (see Supporting Information). Additionally, the EPR spectra of the [Cu(*i*-Pr-pybox)$(H_2O)_2](SbF_6)_2$ (**28**), [Cu(*i*-Pr-pybox)]$(SbF_6)_2$ (**29**), and [Cu(Ph-pybox)$(BnOCH_2CHO)](SbF_6)_2$ (**32**) complexes exhibited well-defined square pyramidal copper centers, in direct accord with the corresponding crystal structures (see Supporting Information).[48] The ratio of $g_{\parallel}/A_{\parallel}$ is indicative of distortion away from square pyramidalization; a value of 126 $\times$ 10^4 for **32** is consistent with negligible amounts of distortion.[49] The above solid- and solution-state data together provide compelling evidence for the presence of complex **31a** (Scheme 6) in the reactions of (benzyloxy)acetaldehyde employing the [Cu(Ph-pybox)]$(SbF_6)_2$ catalyst (**4c**).

Diastereoselectivity Models. The majority of the diastereoselective (benzyloxy)acetaldehyde aldol reactions encountered in this study afford the syn adducts.[50] This syn selectivity can be rationalized by attack of the silylketene acetal on the proposed square pyramidal Cu(II)−aldehyde complex **31a** via an open transition state, which minimizes the number of repulsive gauche and dipole−dipole interactions (Scheme 9, the shielding Ph-(ligand) group has been omitted for clarity).[2c] Of the three

(46) (a) Keck, G. E.; Castellino, S.; Wiley: M. R. *J. Org. Chem.* **1986**, *51*, 5480−5482. (b) Kahn, S. D.; Keck, G. E.; Hehre, W. J. *Tetrahedron Lett.* **1987**, *28*, 279−280. (c) Keck, G. E.; Castellino, S. *Tetrahedron Lett.* **1987**, *28*, 281−284. (d) Keck, G. E.; Andrus, M. B.; Castellino, S. *J. Am. Chem. Soc.* **1989**, *111*, 8136−8141. For evidence supporting chelation of an OTBS group, see: (e) Chen, X.; Hortelano, R. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778−1784.

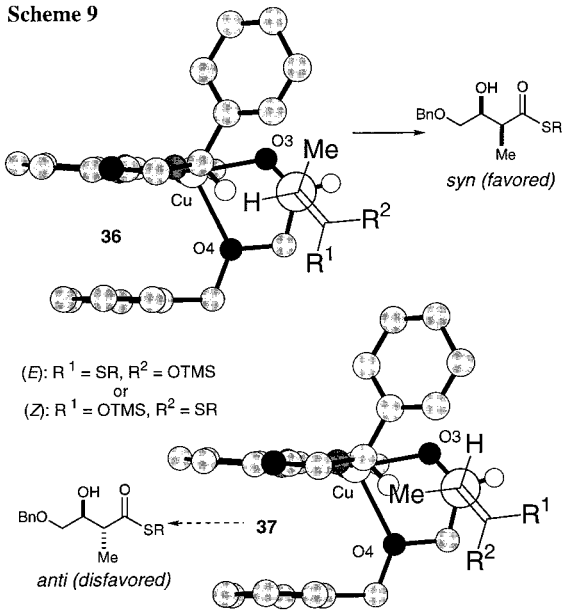
(47) Gennari, C.; Cozzi, P. G. *Tetrahedron* **1988**, *44*, 5965−5974.

(48) The square pyramidal nature of the [Cu(Ph-pybox)$(BnOCH_2CHO)]$-$(SbF6)_2$ spectrum was verified by comparison with the EPR spectra of compounds known to possess square pyramidal copper centers: (a) Reference 42a, p 662. (b) Batra, G.; Mathur, P. *Transition Met. Chem.* **1995,** *20*, 26−29.

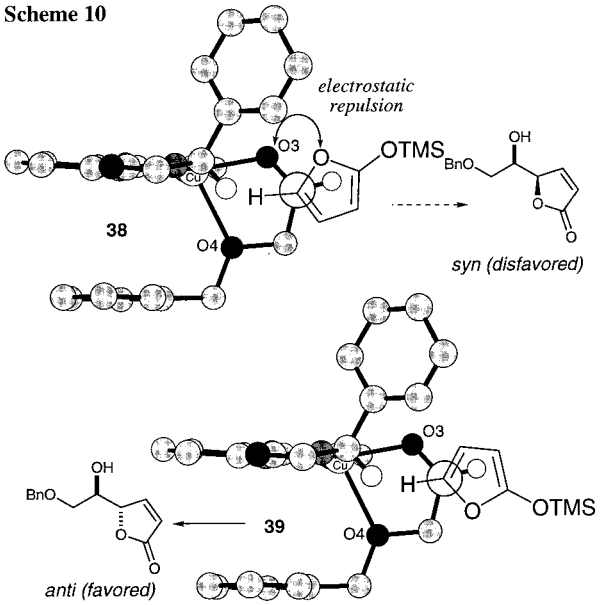
(49) In addition, the simulated spectrum of [Cu(Ph-pybox)$(BnOCH_2$-$CHO)](SbF_6)_2$ closely matched the experimental spectrum (see Supporting Information) when the following simulation parameters were employed: $g_1 = g_2 = 1.9368$, $g_3 = 2.3300$; $A = 152.92$ G, LB = 100 G.

(50) Reetz has observed syn diastereoselectivity in the $TiCl_4$ and $SnCl_4$-mediated aldol reactions of benzyloxyacetaldehyde with propiophenone enolsilanes: Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron* **1984**, *21*, 4327−4336.

Scheme 9



Scheme 10

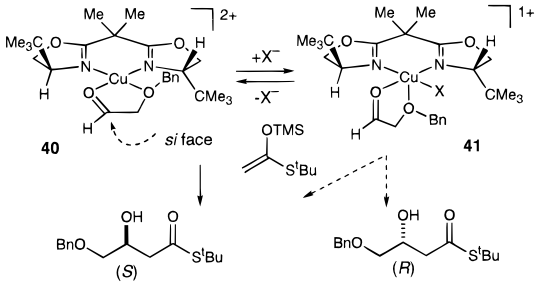


possible transition states that lead to the observed syn product, antiperiplanar transition state **36** has the fewest destabilizing interactions. By comparison, the antiperiplanar transition state **37**, which would afford the anti product, incurs both Me(nucleophile) ↔ CH_2(aldehyde) and Me(nucleophile) ↔ catalyst gauche interactions.

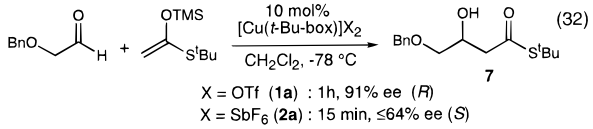
The anti diastereoselectivity observed in the aldol addition of 2-(trimethylsiloxy)furan to (benzyloxy)acetaldehyde (eq 20) may be rationalized through a similar analysis. Inspection of each of the acyclic transition states leads to the conclusion that **38** and **39** are preferred on steric grounds (Scheme 10). Further examination reveals that the synclinal transition state **39** is favored relative to the antiperiplanar transition state **38** due to the electrostatic repulsion between the (benzyloxy)acetaldehyde carbonyl oxygen and the furan oxygen.[24]

Catalyst Characterization and Stereochemical Models: [Cu(*tert*-Bu-box)](OTf)$_2$. Prior work from this laboratory[6] has provided the precedent that the [Cu((*S*,*S*)-*tert*-Bu-box)](OTf)$_2$ and [Cu(*tert*-Bu-box)](SbF$_6$)$_2$ complexes **1a** and **2a** also have the potential to chelate with (benzyloxy)acetaldehyde. The relevant complexes of this substrate with **1** and **2** are illustrated below (Scheme 11). In the absence of counterion participation, complex **40** affords an unequivocal prediction that the stereochemical outcome of the reaction should afford the illustrated (*S*) aldol adduct. If the counterion is an integral part of the aldehyde−catalyst complex, as in **41**, the stereochemical outcome of the reaction is more ambiguous, since aldehyde chelation could occur from either equatorial−equatorial or equatorial−apical (pictured) complexes.

Scheme 11



The data provided below (eq 32) reveal that complex **40** does predict the sense of asymmetric induction when the box−Cu(SbF$_6$)$_2$ complex **2a** is employed but that the opposite sense of induction is observed when the analogous box−Cu(OTf)$_2$ complex **1a** is employed. We thus conclude that, with the current



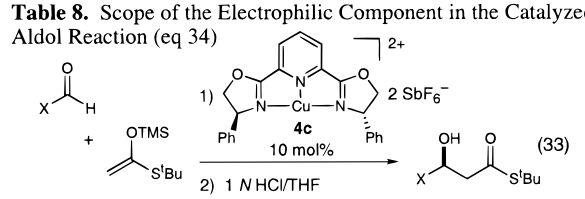
reaction, the triflate counterion remains associated with the metal complex during the catalytic event. This result stands in contrast to the analogous aldol reactions with pyruvate esters, where both **1a** and **2a** afford the same sense of asymmetric induction.[51] It is also noteworthy that the SbF$_6$-derived complex **2a** is less enantioselective than its triflate counterpart. One might speculate that **2a** is too Lewis acidic for this substrate to allow a highly selective process to occur.

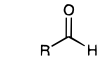
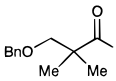
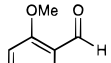
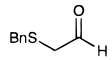
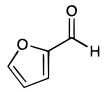
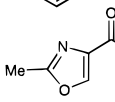
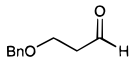
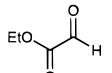
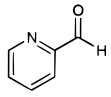
Methodology Limitations

As demonstrated previously, a chelating substrate is necessary to achieve high enantioselectivity in the [Cu((*S*,*S*)-Ph-pybox)](SbF$_6$)$_2$ (**4c**) catalyzed Mukaiyama aldol reaction (eq 33); moreover, there are strict requirements on the nature of the chelating substituent (Table 8). Replacement of the benzyloxy with a benzylthio group, as in (benzylthio)acetaldehyde, resulted in a decline in enantioselection from 99% to 36% ee. Furthermore, alteration of the tether length can have a dramatic impact, as evidenced by the complete loss of enantioselectivity when an additional methylene unit was inserted (β-(benzyloxy)-propionaldehyde). Simple stereochemical models suggest that the five-membered chelate with (benzyloxy)acetaldehyde readily complements the ligand pocket available in [Cu(Ph-pybox)](SbF$_6$)$_2$, whereas the six-membered chelate for β-(benzyloxy)-propionaldehyde adopts a chair or twist-boat conformation, which undergoes significant steric interactions with the pybox ligand framework. The complete lack of selectivity obtained with substrates which, presumably, would attain chelation geometries similar to that of (benzyloxy)acetaldehyde, such as ethyl glyoxylate, is not easily rationalized.

(51) (a) Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893−7894. (b) See ref 25.

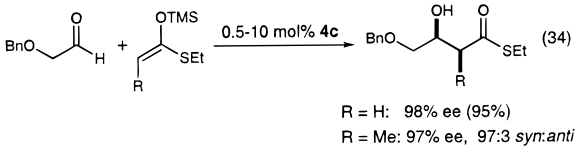
Table 8. Scope of the Electrophilic Component in the Catalyzed Aldol Reaction (eq 34)



substrate	% ee	substrate	% ee	substrate	% ee
	<10		<10		<10
R = Ph, CH(Me)2, CH=CHPh					
	36		<10		9
	<10		<10		<10

Conclusion

In conclusion, efficient catalytic enantioselective Mukaiyama aldol additions to (benzyloxy)acetaldehyde utilizing the C_2-symmetric bis(oxazolinyl)pyridine−Cu(II) complex [Cu((*S*,*S*)-Ph-pybox)](SbF$_6$)$_2$ (**4c**) have been documented. A wide range of silylketene acetal and enolsilane nucleophiles can be employed, utilizing 0.5−10 mol % catalyst loadings, to provide the aldol products in good yield and with high selectivity (eq 34).



Investigation into the reaction mechanism utilizing doubly labeled silylketene acetals indicated that there is a significant intermolecular component to silyl transfer; however, any transient silyl species does not effectively compete with the chiral copper catalyst **4c** at −78 °C. Further mechanistic studies revealed a significant positive nonlinear effect, proposed to arise from the selective formation of the stable [Cu((*S*,*S*)-Ph-pybox)-((*R*,*R*)-Ph-pybox)](SbF$_6$)$_2$ 2:1 ligand:metal complex (**26**). A stereochemical model, **31a**, is proposed in which chelation of (benzyloxy)acetaldehyde to the metal center to form a square pyramidal copper intermediate accounts for the observed sense of induction. Support for this proposal has been gained from double stereodifferentiating reactions, EPR spectroscopy, ESI spectrometry, and, ultimately, the X-ray crystal structure **32** of the aldehyde bound to catalyst.[52]

Experimental Section[53]

General Procedure for the Preparation of Ketene Acetals. The thioester (1 equiv) was added to a cold (−78 °C) 0.4 M solution of lithium diisopropylamide (1.2 equiv) in THF and stirred for 1 h before the addition of chlorotrimethylsilane (1.1 equiv). The reaction mixture was warmed to ambient temperature over a 4-h period, diluted with pentane, washed with phosphate buffer (pH = 7) and 0.5 M aqueous $CuSO_4$, and dried (Na_2SO_4). Removal of the solvent and distillation of the crude liquid under reduced pressure afforded the desired ketene thioacetal.[54]

General Procedure for the Preparation of (*Z*)-Ketene Thioacetals. The Collum procedure[55] was employed for the synthesis of this family of ketene acetals. As a general precaution, freshly dried/distilled reagents were used in order to attain the highest levels of stereoselectivity (>95:5). A chilled (0 °C) slurry of TMP·HBr (1.3 equiv, 0.09 M in THF) was treated with *n*-BuLi (2.4 equiv, 1.6 M in hexanes), stirred for 5 min, and cooled to −78 °C. A solution of the thioester (1.0 equiv, 0.5 M in THF) was cannulated into the light yellow solution and stirred an additional 30 min. Chlorotrimethylsilane (2 equiv) and triethylamine (0.5 equiv) were added, and the solution was warmed to 0 °C over a 4-h period before being diluted with pentane and washed with phosphate buffer (pH = 7) and 0.5 M aqueous $CuSO_4$. The organic layer was dried (Na_2SO_4), concentrated, and distilled under vacuum to furnish the title compounds.

General Procedure for the Preparation of (*E*)-Ketene Thioacetals. The Ireland procedure[56] was employed for the synthesis of this family of ketene acetals. As a general precaution, freshly dried/distilled reagents were used in order to attain the highest levels of stereoselectivity (>95:5). A solution of LDA (1 equiv) and HMPA (23% v/v) was stirred for 10 min prior to cooling (−78 °C) and treatment with the thioester (1.1 equiv). The solution was stirred for 15 min, treated with chlorotrimethylsilane (1 equiv), and warmed slowly to 0 °C. The reaction was diluted with pentane, washed with phosphate buffer (pH = 7) and 0.5 M $CuSO_4$, and dried (Na_2SO_4) prior to concentration under reduced pressure. The unpurified product was distilled under vacuum to furnish the title compounds.

Preparation of [Cu((*S*,*S*)-Phenyl-bis(oxazolinyl)pyridine)](SbF$_6$)$_2$ (4c). To an oven-dried round-bottom flask containing a magnetic stirring bar were added, in a nitrogen atmosphere box, (*S*,*S*)-bis(phenyloxazolinyl)pyridine (18.5 mg, 0.05 mmol) and $CuCl_2$ (6.7 mg, 0.05 mmol). To an oven-dried round-bottom flask containing a magnetic stirring bar was added, in a nitrogen atmosphere box, $AgSbF_6$ (34.4 mg, 0.10 mmol). The flasks were fitted with serum caps and removed from the nitrogen atmosphere box, and the flask containing the ligand/$CuCl_2$ mixture was charged with CH_2Cl_2 (1.0 mL). The resulting suspension was stirred rapidly for 1 h to give a fluorescent green suspension. $AgSbF_6$ (in 0.5 mL CH_2Cl_2) was added via cannula with vigorous stirring, followed by a 0.5-mL CH_2Cl_2 rinse. The resulting mixture was stirred rapidly for 3 h in the absence of light and filtered through an oven-dried glass pipet tightly packed with cotton (or alternatively an oven-dried 0.45-μm PTFE filter) to remove the white AgCl precipitate, yielding active catalyst [Cu(Ph-pybox)](SbF$_6$)$_2$ as a clear blue solution.

General Procedure for the Catalyzed Addition of Silylketene Acetals to Benzyloxyacetaldehyde Using [Cu(Ph-pybox)](SbF$_6$)$_2$ (4c). To a −78 °C solution of [Cu(Ph-pybox)](SbF$_6$)$_2$ in CH_2Cl_2 which was prepared as described above was added benzyloxyacetaldehyde (70.0 μL, 0.50 mmol), followed by a silylketene acetal (0.60 mmol). The resulting solution was stirred at the indicated temperature (−78 or −50 °C, see text) until the aldehyde was completely consumed (15 min−48 h), as determined by TLC (30% EtOAc/hexanes). The reaction mixture was then filtered through a 1.5- × 8-cm plug of silica gel with Et_2O (50 mL). Concentration of the ether solution gave a clear oil, which was dissolved in THF (10 mL) and 1 N HCl (2 mL). After standing at room temperature for 15 min, this solution was poured into a separatory funnel and diluted with Et_2O (10 mL) and H_2O (10 mL). After mixing, the aqueous layer was discarded, and the ether layer was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The resulting ether layer was dried over anhydrous $MgSO_4$, filtered, and concentrated to provide the hydroxy esters.

Preparation of (*S*)-*tert*-Butyl 4-Benzyloxy-3-hydroxybutanethioate (7, Table 4, Entry 1). Compound **7** was prepared according to the general procedure using [Cu(Ph-pybox)](SbF$_6$)$_2$ (200 μL, 2.5 μmol, 0.5 mol %) and the silylketene acetal of *tert*-butyl thioacetate (122 mg, 0.60 mmol, 153 μL) to provide the pure (*S*)-hydroxy ester in 100%

(52) Since completion of this study, other chiral chelating Lewis acid complexes that could well be good catalysts for this family of reactions have been reported: see ref 35.

(53) General information is provided in the Supporting Information.

(54) Ketene silylthioacetal of *tert*-butyl thioester: Gerlach, H.; Kunzler, P. *Helv. Chim. Acta* **1978**, *61*, 2503−2509.

(55) Hall, P. L.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc*. **1991**, *113*, 9571−9574.

(56) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868−2877. We have also occasionally used the Fukuzumi−Otera protocol: Otera, J.; Fujita, Y.; Fukuzumi, S. *Synlett* **1994**, 213-214.

yield (141 mg, 0.50 mmol). Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (94.2:0.8:5.0 hexanes/2-propanol/EtOAc; 1.0 mL/min; (*R*) enantiomer t_r = 16.3 min; (*S*) enantiomer t_r = 17.9 min) or with a Chiralcel AD column (96:4 hexanes/2-propanol; 1.0 mL/min; (*S*) enantiomer t_r = 13.1 min; (*R*) enantiomer t_r = 16.5 min; 99% ee). The analytical data obtained from this material (^{1}H NMR, ^{13}C NMR, IR, and HRMS) were identical to those previously reported:[4c] $[\alpha]^{rt}_D$ −10.9 (*c* 3.0, CH_2Cl_2); $[\alpha]^{26}_D$ (lit.[4c]) +10.0 (*c* 1.0, $CHCl_3$) 96% ee (*R*).

Preparation of (*S*)-Ethyl 4-Benzyloxy-3-hydroxybutanethioate (Table 4, Entry 2). This compound was prepared according to the general procedure employing [Cu(Ph-pybox)]$(SbF_6)_2$ (200 μL, 2.5 μmol, 0.5 mol %) and the silylketene acetal of ethyl thioacetate (106 mg, 0.60 mmol, 132 μL) to provide the pure adol adduct in 95% yield (121 mg, 0.048 mmol) after flash chromatography with 20% EtOAc/hexanes. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98:2 hexanes/2-propanol; 1.0 mL/min): (*S*) enantiomer t_r = 31.6 min; (*R*) enantiomer t_r = 35.7 min; 98% ee. The analytical data obtained from this material (^{1}H NMR, ^{13}C NMR, and HRMS) were identical to those previously reported:[4c] $[\alpha]^{rt}_D$ −10.6 (*c* 4.2, CH_2Cl_2); $[\alpha]^{26}_D$ (lit.[4c]) +11.4 (*c* 1.0, $CHCl_3$), 94% ee (*R*).

Preparation of (*S*)-Ethyl 4-Benzyloxy-3-hydroxybutanoate (Table 4, Entry 3). The silyl ether was prepared according to the general procedure employing [Cu(Ph-pybox)]$(SbF_6)_2$ (200 μL, 2.5 μmol, 0.5 mol %) and the silylketene acetal of EtOAc (96 mg, 0.60 mmol, 114 μL). Deprotection of the TMS ether using 1 N HCl caused decomposition to the retroaldol product; thus, a fluoride deprotection procedure was used instead. The crude silyl ether was dissolved in THF (5 mL) and cooled to 0 °C. TBAF (1.0 M in THF, 0.60 mmol, 0.60 mL) was added dropwise. After 15 min, the solution was diluted with Et_2O (10 mL) and saturated $NaHCO_3$ (10 mL) and poured into a separatory funnel. After mixing, the aqueous layer was discarded and the organic layer washed with brine (10 mL) and dried over $MgSO_4$. Filtration and concentration gave the pure hydroxy ethyl ester in 99% yield (117 mg, 0.49 mmol) after flash chromatography with 20% EtOAc/hexanes. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (94.2:0.8:5.0 hexanes/2-propanol/EtOAc; 1.0 mL/min): (*S*) enantiomer t_r = 24.8 min; (*R*) enantiomer t_r = 29.3 min; 98% ee; R_f 0.27 (30% EtOAc/hexanes); $[\alpha]^{rt}_D$ −8.8 (*c* 2.1, CH_2Cl_2); IR (CH_2Cl_2) 3579, 3061, 2905, 1728, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5H), 4.56 (s, 2H), 4.24 (dq, *J* = 4.6, 6.1 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.51 (dd, *J* = 4.5, 9.6 Hz, 1H), 3.47 (dd, *J* = 6.0, 9.6 Hz, 1H), 2.96 (br s, 1H), 2.54 (d, *J* = 6.3 Hz, 2H), 1.25 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 137.8, 128.3, 127.7, 127.6, 73.2, 73.0, 67.1, 60.6, 38.2, 14.0; HRMS (EI) exact mass calcd for $C_{13}H_{18}O_4^+$ requires *m*/*z* 238.1205, found *m*/*z* 238.1206.

Preparation of (*S*)-(3-Benzyloxy-2-hydroxypropyl)-2,2-dimethyl-1,3-dioxin-4-one (11, Eq 12). Compound **11** was prepared according to the general procedure using [Cu(Ph-pybox)]$(SbF_6)_2$ (2 mL, 0.025 mmol, 5 mol %) and the trimethylsilylketene acetal derived from 2,2,6-trimethyl-1,3-dioxen-4-one[15] (126 mg, 0.60 mmol) to provide the pure adol adduct in 95% yield (165 mg, 0.564 mmol) after flash chromatography with 50% EtOAc/hexanes. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexanes/2-propanol; 1.0 mL/min): (*R*) enantiomer t_r = 17.7 min; (*S*) enantiomer t_r = 22.6 min; 92% ee; R_f 0.20 (50% EtOAc/hexanes); $[\alpha]^{rt}_D$ −15.1, $[\alpha]^{rt}_{546}$ −14.9 (*c* 1.3, $CHCl_3$); IR (neat) 3438, 3089, 2914, 2863, 1718, 1634 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5H), 5.31 (s, 1H), 4.56 (s, 2H), 4.10 (m, 1H), 3.51 (dd, *J* = 3.6, 9.4 Hz, 1H), 3.40 (dd, *J* = 6.5, 9.4 Hz, 1H), 2.40 (dd, *J* = 1.5, 5.4 Hz, 1H), 2.39 (dd, *J* = 3.1, 5.4 Hz, 1H), 1.66 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 161.1, 137.6, 128.6, 128.5, 128.1, 127.9, 106.7, 95.3, 67.5, 60.4, 37.9, 25.4, 24.7; HRMS (CI, NH_3) exact mass calcd for $(C_{16}H_{20}O_5 + NH_4)^+$ requires *m*/*z* 310.1664, found *m*/*z* 310.1654.

Preparation of (3*S*,5*S*)-Methyl 6-Benzyloxy-3,5-dihydroxyhexanoate (13, Eq 13). A clear blue solution of [Cu(Ph-pybox)]$(SbF_6)_2$ (2.0 mL, 0.05 mmol, 0.75 mol %) was added over 15 min to a −78 °C solution of benzyloxyacetaldehyde (1.0 g, 6.7 mmol) and the bis silylketene acetal of methyl acetoacetate[17] (2.1 g, 8.0 mmol) in CH_2Cl_2 (2 mL). After 2 h at −78 °C, TLC indicated complete consumption of starting aldehyde (R_f 0.13, 20% EtOAc/hexanes) and a new higher R_f spot (R_f 0.39, 20% EtOAc/hexanes). The reaction mixture was then filtered through a 2.5- × 8-cm plug of silica gel with Et_2O (200 mL). Concentration of the ether solution gave a clear oil, which was dissolved in THF (100 mL) and 1 N HCl (10 mL). After standing at room temperature for 15 min, this solution was poured into a separatory funnel and diluted with Et_2O (100 mL). The aqueous layer was discarded and the organic layer washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL) and dried over anhydrous $MgSO_4$. Filtration and concentration of the resulting solution gave the hydroxy ketoester in 96% yield (1.7 g, 6.4 mmol): R_f 0.50 (50% EtOAc/hexanes); $[\alpha]^{rt}_D$ −13.7 (*c* 3.55, $CHCl_3$); IR (neat) 3438, 2864, 1740, 1716 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 5H), 4.54 (s, 2H), 4.30 (m, 1H), 3.65 (s, 3H), 3.50 (dd, *J* = 4.5, 9.6 Hz, 1H), 3.41 (dd, *J* = 5.7, 9.6 Hz, 1H), 2.78 (d, *J* = 5.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.3, 168.6, 137.8, 128.5, 127.9, 127.8, 73.5, 73.1, 66.8, 52.4, 49.7, 46.3; HRMS (CI, NH_3) exact mass calcd for $(C_{14}H_{18}O_5 + NH_4)^+$ requires *m*/*z* 284.1487, found *m*/*z* 284.1498.

The hydroxy ketoester was subsequently reduced to the anti diol using tetramethylammonium acetoxyborohydride.[57] A solution of tetramethylammonium acetoxyborohydride (11.8 g) in acetic acid (60 mL) was added to a −35 °C solution of the ketoester in CH_3CN (100 mL) over 30 min. The resultant milky white solution was stirred at −35 °C for 18 h and then quenched by the addition of a saturated solution of Rochelle salts (100 mL) and warming to room temperature. The resulting mixture was diluted with EtOAc and made basic with a saturated solution of Na_2CO_3. The aqueous layer was discarded, and the organic layer was washed with brine (50 mL), dried over $MgSO_4$, and concentrated to give the anti diol in 91% yield (1.6 g, 6.1 mmol) as a white solid. Product ratios were determined by HPLC with a Chiralcel OD-H column (90:10 hexanes/2-propanol; 1.0 mL/min): *syn*-(3*R*,5*S*) t_r = 15.9 min; *anti*-(3*R*,5*R*) t_r = 17.9 min; *syn*-(3*S*,5*R*) t_r = 22.8 min; *anti*-(3*S*,5*S*) t_r = 29.5 min; 15:1 anti:syn, 97% anti ee: mp 61 °C; R_f 0.40 (50% EtOAc/hexanes); $[\alpha]^{rt}_D$ +2.2; $[\alpha]^{rt}_{546}$ +6.3 (c 1.8, $CHCl_3$); IR (CH_2Cl_2) 3417 (br) 3030, 2949, 2863, 1734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H), 4.56 (s, 2H), 4.34 (m, 1H), 4.14 (m, 1H), 3.57 (s, 3H), 3.46 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.41 (dd, *J* = 9.7, 7.5 Hz, 1H), 3.01 (s, 1H); 2.51 (d, *J* = 5.8 Hz, 1H); 1.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 138.6, 134.7, 128.5, 127.9, 74.3, 73.4, 68.2, 66.3, 52.1, 41.3, 38.8; HRMS (CI, NH_3) exact mass calcd for $(C_{14}H_{20}O_5 + NH_4)^+$ requires *m*/*z* 286.1658, found *m*/*z* 286.1654.

Large-Scale Preparation of (*R*)-*tert*-Butyl 6-Benzyloxy-5-hydroxy-3-oxohexanoate and Recovery of Ligand (15, Eq 14). In a nitrogen atmosphere glovebox, an oven-dried 250-mL round-bottom flask equipped with a magnetic stirring bar and an oven-dried 25-mL round-bottom flask were charged with anhydrous $CuCl_2$ (239 mg, 1.8 mmol) and $AgSbF_6$ (1.22 g, 3.6 mmol), respectively. The flasks were sealed with rubber septa, removed from the glovebox, and charged with CH_2Cl_2 (58 mL and 8 mL, respectively) under a positive pressure of nitrogen. To the resulting suspension of $CuCl_2$ was added solid (*R*,*R*)-bis(phenyloxazolinyl)pyridine (657 mg, 1.8 mmol) in one portion. The suspension was rapidly stirred for 2 h, during which time the insoluble material changed color from brown to dark green to light green. To this suspension was rapidly added the $AgSbF_6$ solution via syringe. The suspension was stirred vigorously in the absence of light for 1 h. The resultant suspension (a blue solution containing a fine white precipitate) was sequentially filtered open to the atmosphere through a plug of packed cotton (20 mm × 20 mm) and two oven-dried 0.45-μm filters (Gelman Acrodisc CR PTFE, 25 mm) directly into a dry 250-mL round-bottom flask to give a deep-blue catalyst solution which was used within 2 h.

The above catalyst solution (5 mol %) was cooled to −78 °C under an atmosphere of dry nitrogen. To this solution was added freshly distilled 1,3-bis(trimethylsiloxy)-1-*tert*-butoxybuta-1,3-diene[19,58] (12.6 g, 39.1 mmol) to give a purple solution. This solution was further cooled to −93 °C (internal temperature) via a MeOH/liquid nitrogen cold bath,

(57) Evans, D. A.; Gauchet-Prunet, J. A.; Carreira, E. M.; Charette, A. B. *J. Org. Chem.* **1991**, *56*, 741−750.

(58) Careful distillation is required in order to minimize thermal isomerization to the undesired isomer (bp 50 °C at 0.1 mmHg, bath temp ≤ 65 °C). See: Anderson, G.; Cameron, D. W.; Feutrill, G. I.; Read, R. W. *Tetrahedron Lett.* **1981**, *22*, 4347−4348.

at which point the solution turned brown. Freshly distilled benzyloxyacetaldehyde (5 mL, 35.5 mmol) was added dropwise via syringe pump over 15 min (0.33 mL/min). After addition, the internal reaction temperature had risen to −85 °C. After 5 min at this temperature and 15 min at −78 °C, TLC analysis (30% EtOAc/hexanes) indicated consumption of the starting aldehyde (R_f 0.25). The cold reaction mixture was poured directly onto a deactivated (5% Et_3N/hexanes) silica gel plug (5.5 cm × 12 cm) and eluted rapidly with Et_2O (1.5 L). The filtrate was concentrated in vacuo to yield a yellow oil.

The yellow oil was dissolved in 100 mL of anhydrous MeOH and treated with pyridinium *p*-toluenesulfonate (500 mg). When hydrolysis was complete (1−2 h) by TLC (SM R_f 0.51; 30% EtOAc/hexanes), the volatiles were removed in vacuo, and the yellow oil obtained was purified by flash chromatography with 20−70% EtOAc/hexanes to provide a keto−enol tautomeric mixture of *tert*-butyl (*R*)-6-benzyloxy-5-hydroxy-3-oxohexanoate (keto R_f 0.19, enol R_f 0.11; 30% EtOAc/hexanes) as a yellow oil in 85% yield (9.37 g, 30.2 mmol).[21]

A small sample (ca. 1−2 mg) of the purified product was converted to the Mosher ester by the method of Ward and Rhee ((*S*)-MTPA-Cl, DMAP, CH_2Cl_2).[59] This material was directly analyzed by HPLC with a Zorbax SIL column (5% EtOAc/hexanes;, 1.0 mL/min): (*S*,*R*) diastereomer t_r = 22.7 min; (*R*,*R*) diastereomer t_r = 26.2 min; ≥99% de.

The original silica plug used to remove the copper catalyst was flushed with 750 mL of 20% concentrated NH_4OH/MeOH and the filtrate concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (100 mL) and concentrated NH_4OH (100 mL), and the layers were separated. The organic layer was washed with concentrated NH_4OH (2 × 100 mL each), water (100 mL), and brine (100 mL). The organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give crude recovered ligand in 62% yield (410 mg, 1.1 mmol) as a waxy yellow solid.

***tert*-Butyl (3*R*,5*R*)-6-Benzyloxy-3,5-dihydroxyhexanoate (16, Eq 15).** To a cooled (−33 °C) solution of 6.64 g (25.2 mmol, 3.4 equiv) of $Me_4NHB(OAc)_3$ in 60 mL of 1:1 MeCN/AcOH was added a solution of *tert*-butyl (*R*)-6-benzyloxy-5-hydroxy-3-oxohexanoate in 10 mL of MeCN via cannula (plus a 5-mL rinse). The reaction was stirred at −33 °C for 42 h, warmed to 0 °C, stirred for 30 min, and then quenched with 50 mL of saturated Na/K tartrate. The mixture was stirred at room temperature for 1 h and then poured into 200 mL of 3:1 EtOAc/H_2O. The mixture was made basic (to pH 8) with solid Na_2CO_3, and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 40 mL), and the organic extracts were combined and washed with brine (1 × 40 mL) before being dried over $MgSO_4$ and concentrated in vacuo. The residue was purified via flash chromatoraphy (40% EtOAc/hexanes) to afford 1.95 g (84% yield) of the desired diol as a clear, colorless oil which solidified upon storage at −20 °C: $[\alpha]_D$ −8.3 (c 1.0, CH_2Cl_2); IR (thin film) 3437 (br), 3030−2863, 1726 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5H), 4.55 (s, 2H), 4.27 (tt, 1H, J = 6.8, 5.3 Hz), 4.12 (tt, 1H, J = 7.4, 4.2 Hz,), 3.50 (dd, 1H, J = 9.5, 3.9 Hz), 3.40 (dd, 1H, J = 9.5, 7.3 Hz), 3.17 (br s, 2H), 2.42−2.40 (m, 2H), 1.62−1.56 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 138.0, 128.5, 127.8, 127.7, 81.3, 74.4, 73.3, 67.6, 65.4, 42.5, 38.8, 28.1; exact mass calcd for $C_{17}H_{26}O_5$ + Na requires *m*/*z* 333.1678, found *m*/*z* 333.1687 (FAB, *m*-nitrobenzyl alcohol, added NaI).

***tert*-Butyl (3*S*,5*R*)-6-Benzyloxy-3,5-dihydroxyhexanoate (17, Eq 16).** To a solution of *tert*-butyl (*R*)-6-benzyloxy-5-hydroxy-3-oxohexanoate (9.20 g, 29.8 mmol) in 300 mL of THF and 60 mL of methanol was added diethylmethoxyborane (4.7 mL, 36 mmol), and the solution was stirred for 15 min at room temperature before being cooled to −78 °C. Sodium borohydride (1.6 g, 42 mmol) is added portionwise over a 10-min period (moderate gas evolution observed). After the solution was stirred for 10 h at −78 °C, 120 mL of 30% aqueous hydrogen peroxide was slowly added to the cold solution via addition funnel. The mixture was allowed to stir while warming to room temperature over 10 h and then partioned between EtOAc and water. The aqueous layer was extracted 3× with EtOAc (200 mL) and then the combined organics were washed successively 2× with saturated $NaHCO_3$ (200 mL), then water (200 mL), saturated Na_2SO_3 (200 mL), and saturated NaCl (200 mL) before being dried over Na_2SO_4 and concentrated in vacuo to a viscous pale yellow oil. This material is sufficiently pure for further transformations. Flash chromatography (40% → 50% EtOAc/hexanes) provided the desired product (>200:1 syn:anti) as a colorless oil (7.82 g, 85%). HPLC Chiralcel AD analysis (1.0 mL/min; 93:7 hexanes/2-propanol): (3*R*,5*S*) t_r = 14.1 min (desired); (3*S*,5*R*) t_R = 18.8 min; (3*R*,5*R*) and (3*S*,3*S*) t_R = 15.2 and 19.4 min (exact assignment undetermined for anti diols). The analytical data obtained from this material are consistent with those previously reported.[21]

Preparation of (2*S*,3*S*)-Ethyl 4-Benzyloxy-3-hydroxy-2-methylbutanethioate (Table 5, Entry 1). This compound was prepared according to the general procedure employing [Cu(Ph-pybox)]$(SbF_6)_2$ (3.0 mL, 0.05 mmol, 10 mol %) and the silylketene acetal of ethyl thiopropionate as a 95:5 mixture of *Z*:*E* isomers (114 mg, 0.60 mmol, 130 μL). The product was obtained as a clear oil in 90% yield (121 mg, 0.45 mmol) after flash chromatography with 20% EtOAc/hexanes. Product ratios were determined by HPLC with a Chiralcel OD-H column (95.5:1.5:3 hexanes/2-propanol/EtOAc; 1.0 mL/min): *syn*-(2*S*,3*S*) t_r = 12.6 min; *syn*-(2*R*,3*R*) t_r = 14.3 min; *anti*-(2*R*,3*S*) t_r = 15.2 min; *anti*-(2*S*,3*R*) t_r = 17.5 min; 97:3 syn:anti; 97% syn ee. The analytical data obtained from this material (^1H NMR, ^{13}C NMR, and HRMS) were identical to those previously reported:[4c] $[\alpha]^{rt}_D$ +41.1 (*c* 3.6, CH_2Cl_2); $[\alpha]^{26}_D$ (lit.[4c]) −3.3 (*c* 1.0, $CHCl_3$); syn:anti 72:28, 90% syn ee (2*R*,3*R*).

Preparation of (2*S*,3*S*)-Ethyl 4-Benzyloxy-3-*tert*-butyldimethylsiloxy-2-methylbutanethioate (Table 5, Entry 3). The silyl ether-protected adduct could also be obtained directly, according to the general procedure employing [Cu(Ph-pybox)]$(SbF_6)_2$ (3.0 mL, 0.05 mmol, 10 mol %) and the *tert*-butyldimethylsilylketene acetal of ethyl thiopropionate as a 94:6 mixture of *Z*:*E* isomers (139 mg, 0.60 mmol, 161 μL). The silyl ether product (after filtration away from the copper catalyst through SiO_2) was not subjected to the deprotection procedure in the general procedure but was purified by flash chromatography with 0−30% EtOAc/hexanes. A small amount of the alcohol adduct (<10%, not isolated in pure form) was obtained, but the major product was the *tert*-butyldimethylsilyl ether, which was obtained as a clear oil in 68% yield (130 mg, 0.34 mmol): $[\alpha]^{rt}_D$ +12.46 (*c* 0.92, CH_2Cl_2); IR (CH_2Cl_2) 2931, 2858, 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5H), 4.54 (d, J = 12.0 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.21 (app q, J = 5.5 Hz, 1H), 3.41 (d, J = 5.7 Hz, 2H), 2.88 (dq, J = 5.2, 6.9 Hz, 1H), 2.84 (q, J = 7.4 Hz, 2H), 1.22 (t, J = 7.4 Hz, 3H), 1.17 (d, J = 6.9 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 138.1, 128.3, 127.6, 127.5, 73.2, 72.5, 72.3, 51.6, 25.8, 23.1, 18.1, 14.6, 11.8, −4.4, −5.0; LRMS (FAB/NBA + NaI) *m*/*z* 405 MNa^+; HRMS (FAB/NBA + NaI) exact mass calcd for $(C_{20}H_{34}O_3SiS+Na)^+$ requires *m*/*z* 405.1896, found *m*/*z* 405.1891. Product ratios were determined after conversion to the alcohol with aqueous HF in MeCN. The combined silyl ether and alcohol products in MeCN (1.5 mL) were treated with 40% HF/H_2O (0.5 mL). After 30 min, TLC (30% EtOAc/hexanes) indicated complete consumption of the silyl ether, and the reaction mixture was quenched with saturated $NaHCO_3$ (5 mL). The resultant mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to provide the hydroxy ester. Purification by flash chromatography with 10−20% EtOAc/hexanes provided the title compound as a clear, colorless oil in 70% yield (93 mg, 0.35 mmol). The analytical data obtained from this material (^1H NMR, ^{13}C NMR, and HRMS) were identical to those described above for the alcohol obtained from the corresponding trimethylsilyl ether. Product ratios were determined for the alcohol by HPLC with a Chiralcel OD-H column (95.5:1.5:3 hexanes/2-propanol/EtOAc; 1.0 mL/min): *syn*-(2*S*,3*S*) t_r = 12.6 min; *syn*-(2*R*,3*R*) t_r = 14.3 min; *anti*-(2*R*,3*S*) t_r = 15.2 min; *anti*-(2*S*,3*R*) t_r = 17.5 min; 93:7 syn:anti; 96% syn ee.

(2*S*,3*S*)-Ethyl 4-Benzyloxy-3-hydroxy-2-isobutylbutanethioate (Table 5, Entry 4). This compound was prepared according to the general procedure employing [Cu(Ph-pybox)]$(SbF_6)_2$ (3.0 mL, 0.05 mmol, 10 mol %) and the silylketene acetal derived from ethyl 4-methylpentanethioate as a 90:10 mixture of *Z*:*E* isomers (174 μL, 0.60 mmol) to provide the pure product as a clear oil in 85% yield

(59) Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.* **1991**, *32*, 7165−7166.

(132 mg, 0.43 mmol) after flash chromatography with 10−20% EtOAc/hexanes. Product ratios were determined by HPLC with a Chiralcel AD column (99:1 hexanes/2-propanol; 1.0 mL/min): *syn*-(2*R*,3*R*) t_r = 19.7 min; *syn*-(2*S*,3*S*) t_r = 21.1 min; *anti*-enantiomers t_r = 23.5, 24.4 min; 95:5 syn:anti, 95% syn ee; $[\alpha]^{rt}_D$ +11.48 (c 4.8, CH_2Cl_2). Syn isomer: IR (CH_2Cl_2) 3685, 3569, 2960, 2871, 1677, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 5H, Ph), 4.55 (d, J = 11.8 Hz, 1H), 4.52 (d, J = 11.8 Hz, 1H), 3.92 (dt, J = 3.8, 6.6 Hz, 1H), 3.53 (dd, J = 3.8, 9.6 Hz, 1H), 3.45 (dd, J = 6.6, 9.6 Hz, 1H), 2.90 (ddd, J = 3.6, 6.7, 10.7 Hz, 1H), 2.87 (q, J = 7.4 Hz, 2H), 2.41 (br s, 1H), 1.73 (ddd, J = 4.1, 10.8, 13.3 Hz, 1H), 1.58 (dd septet, J = 4.1, 10.0, 6.6 Hz, 1H), 1.47 (ddd, J = 3.6, 9.8, 13.3 Hz, 1H), 1.23 (t, J = 7.4 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1, 137.7, 128.4, 127.8(2), 73.4, 71.6, 71.5, 55.1, 37.7, 25.9, 23.7, 23.4, 21.6, 14.5; LRMS (CI/NH_3) *m*/*z* 311 $(MH)^+$, 328 $(M + NH_4)^+$; HRMS (CI/NH_3) exact mass calcd for $(C_{17}H_{26}O_3S + NH_4)^+$ requires *m*/*z* 328.1946, found *m*/*z* 328.1949.

Preparation of (2*S*,3*S*)-*tert*-Butyl 4-Benzyloxy-3-hydroxy-2-methylbutanethioate (Table 5, Entry 5). This compound was prepared according to the general procedure employing [Cu(Ph-pybox)]$(SbF_6)_2$ (2.0 mL, 0.05 mmol, 10 mol %) and the silylketene acetal of *tert*-butyl thiopropionate as a 95:5 mixture of *Z*:*E* isomers (131 mg, 0.60 mmol, 149 μL). The product was obtained as a clear oil in 86% yield (127 mg, 0.43 mmol) after flash chromatography with 10−20% EtOAc/hexanes. Product ratios were determined by HPLC with a Chiralcel OD-H column (99:1 hexanes/2-propanol; 1.0 mL/min): *syn*-(2*R*,3*R*) t_r = 14.7 min; *syn*-(2*S*,3*S*) t_r = 15.9 min; *anti*-(2*S*,3*R*) t_r = 17.3 min; *anti*-(2*R*,3*S*) t_r = 20.9 min; 85:15 syn:anti; 99% syn ee. The analytical data obtained from this material (^1H NMR, ^{13}C NMR, and HRMS) were identical to those previously reported:[4c] $[\alpha]^{rt}_D$ +40.9 (*c* 3.8, CH_2Cl_2); $[\alpha]^{26}_D$ (lit.[4c]) +10.3° (*c* 1.0, $CHCl_3$); syn:anti 8:92; 90% anti ee (2*S*,3*R*).

Preparation of (2*S*,3*S*)-Ethyl 4-Benzyloxy-3-hydroxy-2-methylbutanoate (Table 5, Entry 7). This compound was prepared according to the general procedure employing [Cu(Ph-pybox)]$(SbF_6)_2$ (3.0 mL, 0.05 mmol, 10 mol %) and the silylketene acetal of ethyl propionate as an 85:15 mixture of *E*:*Z* isomers (131 mg, 0.75 mmol, 163 μL), except that the reaction was performed at −95 °C (liquid N_2/hexanes bath). The product was obtained as a clear oil in 60% yield (76 mg, 0.30 mmol) after flash chromatography with 10−20% EtOAc/hexanes. Deprotection of the TMS ether using 1 N HCl also caused retroaldol reaction, as observed by TLC (30% EtOAc/hexanes). This decomposition accounts for the low yield, as ^1H NMR indicated 95% conversion. Product ratios were determined by HPLC with a Chiralcel OD-H column (90:10 hexanes/EtOAc; 0.5 mL/min): *syn*-(2*R*,3*R*) t_r = 27.8 min; *syn*-(2*S*,3*S*) t_r = 29.8 min; *anti*-(2*S*,3*R*) t_r = 31.1 min; *anti*-(2*R*,3*S*) t_r = 32.8 min; 84:16 syn:anti; 87% syn ee; $[\alpha]^{rt}_D$ +7.78° (*c* 3.6, CH_2Cl_2). Syn isomer: IR (CH_2Cl_2) 3684, 3581, 3060, 2932, 2863, 1727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 5H), 4.56 (d, J = 12.0 Hz, 1H), 4.53 (d, J = 12.0 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 4.07 (app q, J = 5.6 Hz, 1H), 3.52 (dd, J = 4.6, 9.5 Hz, 1H), 3.48 (dd, J = 6.2, 9.5 Hz, 1H), 2.75 (br s, 1H), 2.65 (dq, J = 5.6, 7.2 Hz, 1H), 1.24 (t, J = 7.2 Hz, 3H), 1.21 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 137.8, 128.4, 127.8, 127.7, 73.4, 71.6, 70.9, 60.6, 42.0, 14.1, 11.9; LRMS (CI/NH_3) *m*/*z* 253 $(MH)^+$, 270 $(M + NH_4)^+$; HRMS (CI/NH_3) exact mass calcd for $(C_{14}H_{20}O_4 + H)^+$ requires *m*/*z* 253.1440, found *m*/*z* 253.1437.

(2*S*,3*R*)-Ethyl 2,4-Bis(benzyloxy)-3-hydroxybutanethioate (Table 5, Entry 9). This compound was prepared according to the general procedure employing [Cu(Ph-pybox)]$(SbF_6)_2$ (2.0 mL, 0.05 mmol, 10 mol %) and the silylketene acetal derived from ethyl benzyloxythioacetate as a 90:10 mixture of *Z*:*E* isomers (168 μL, 0.60 mmol) to provide the pure product as a clear oil in 50% yield (93 mg, 0.25 mmol) after flash chromatography with 30% EtOAc/hexanes. Product ratios were determined by HPLC with a Chiralcel OD-H column (89.3:0.7:10 hexanes/2-propanol/EtOAc; 1.0 mL/min): *syn*-(2*S*,3*R*) t_r = 16.2 min; *syn*-(2*R*,3*S*) t_r = 17.0 min; *anti*-(2*R*,3*R*) t_r = 18.0 min; *anti*-(2*S*,3*S*) t_r = 23.1 min; 74:26 syn:anti; 76% syn ee; $[\alpha]_D^{rt}$ −51.0 (*c* 1.5, CH_2Cl_2). Syn isomer: IR (CH_2Cl_2) 3569, 3056, 2933, 2872, 1677 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 10H), 4.84 (d, J = 11.1 Hz, 1H), 4.51 (d, J = 11.9 Hz, 1H), 4.46 (d, J = 11.1 Hz, 1H), 4.45 (d, J = 11.9 Hz, 1H), 4.13 (d, J = 3.5 Hz, 1H), 4.10 (dt, J = 3.7, 5.6 Hz, 1H), 3.53 (dd, J = 5.4, 9.6 Hz, 1H), 3.48 (dd, J = 6.0, 9.6 Hz, 1H), 2.90 (m, 2H), 2.44 (br s, 1H), 1.26 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 137.8, 136.7, 128.5, 128.4 (2), 128.3, 127.8, 127.7, 84.0, 74.3, 73.3, 71.5, 70.0, 22.7, 14.4; LRMS (CI/NH_3) *m*/*z* 361 $(MH)^+$, 378 $(M + NH_4)^+$; HRMS (CI/NH_3) exact mass calcd for $(C_{20}H_{25}O_4S + H)^+$ requires *m*/*z* 361.1474, found *m*/*z* 361.1476.

Preparation of (1′*S*,4*S*)-4-(2′-Benzyloxy-1′-hydroxyethyl)-2-oxacyclopentan-1-one (20, Eq 19). Compound **20** was prepared according to the general procedure employing [Cu(Ph-pybox)]$(SbF_6)_2$ (3.0 mL, 0.05 mmol, 10 mol %) and the silylketene acetal derived from γ-butyrolactone (106 μL, 0.60 mmol) to provide the pure product as a white powder in 95% yield (112 mg, 0.47 mmol) after flash chromatography with 50% EtOAc/hexanes. Product ratios were determined by HPLC with a Chiralcel OD-H column (90:10 hexanes/2-propanol; 1.0 mL/min): *syn*-(1′*R*,4*R*) t_r = 15.6 min; *syn*-(1′*S*,4*S*) t_r = 18.3 min; anti enantiomers t_r = 20.9 min, 27.0 min; 96:4 syn:anti; 95% syn ee; $[\alpha]^{rt}_D$ −8.34 (*c* 4.3, CH_2Cl_2). Syn isomer: mp 47.0−48.0 °C (white powder, racemic); IR (CH_2Cl_2) 3672, 3600, 3056, 2923, 2862, 1764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H), 4.57 (d, J = 11.9 Hz, 1H), 4.52 (d, J = 11.9 Hz, 1H), 4.35 (dt, J = 3.2, 8.8 Hz, 1H), 4.31 (m, 1H), 4.17 (dt, J = 7.2, 9.1 Hz, 1H), 3.53 (d, J = 5.7 Hz, 2H), 3.51 (br s, 1H), 2.73 (dt, J = 3.7, 9.6 Hz, 1H), 2.36 (dq, J = 12.6, 9.3 Hz, 1H), 2.15 (dddd, J = 3.2, 7.2, 9.4, 12.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 137.6, 128.3, 127.7, 127.6, 73.2, 71.9, 68.0, 67.0, 42.4, 22.3; LRMS (EI) *m*/*z* 236 $(M)^+$; HRMS (EI) exact mass calcd for $(C_{13}H_{16}O_4)^+$ requires *m*/*z* 236.1049, found *m*/*z* 236.1040.

Preparation of (1′*R*,4*S*)-4-(2′-Benzyloxy-1′-hydroxyethyl)-cyclopent-2-enone (21, Eq 20). Compound **21** was prepared according to the general procedure employing [Cu(Ph-pybox)]$(SbF_6)_2$ (3.0 mL, 0.05 mmol, 10 mol %) and 2-(trimethylsilyloxy)furan[24] (101 μL, 0.60 mmol) to provide the pure product as a clear oil in 90% yield (106 mg, 0.45 mmol) after flash chromatography with 60% EtOAc/hexanes. Product ratios were determined by HPLC with a Chiralcel OD-H column (90:10 hexanes/2-propanol; 1.0 mL/min; *anti*-(1′*S*,4*R*) t_r = 16.7 min; syn enantiomers t_r = 21.8 min, 23.0 min; *anti*-(1′*R*,4*S*) t_r = 26.1 min; 91:9 anti:syn; 92% anti ee; $[\alpha]^{rt}_D$ −77.1 (*c* 5.1, CH_2Cl_2). Anti isomer: IR (CH_2Cl_2) 3682, 3569, 3067, 2913, 2872, 1790, 1759, 1161, 1090, 1045 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, J = 1.3, 5.7 Hz, 1H), 7.33 (m, 5H), 6.16 (dd, J = 1.8, 5.7 Hz, 1H), 5.05 (dt, J = 6.9, 1.7 Hz, 1H), 4.60 (d, J = 11.9 Hz, 1H), 4.57 (d, J = 11.8 Hz, 1H), 3.76 (dt, J = 6.8, 3.8 Hz, 1H), 3.73 (dd, J = 3.7, 9.5 Hz, 1H), 3.70 (dd, J = 4.2, 9.5 Hz, 1H), 2.71 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 155.1, 137.3, 128.6, 128.1, 127.9, 122.1, 82.7, 73.7, 71.3, 70.4; LRMS (CI/NH_3) *m*/*z* 235 $(MH)^+$, 252 $(M + NH_4)^+$; HRMS (CI/NH_3) exact mass calcd for $(C_{13}H_{14}O_4 + NH_4)^+$ requires *m*/*z* 252.1236, found *m*/*z* 252.1238.

Preparation of (*S*)-5-Benzyloxy-4-hydroxypentan-2-one (Table 6, Entry 1). This compound was prepared according to the general procedure employing [Cu(Ph-pybox)]$(SbF_6)_2$ (4.0 mL, 0.10 mmol, 100 mol %); except that less benzyloxyacetaldehyde (14 μL, 0.10 mmol) and the enolsilane of acetone (33 μL, 0.20 mmol) were used. The pure product was obtained as a clear oil in 96% yield (20 mg, 96 μmol) after flash chromatography with 40% EtOAc/hexanes. Enantiomeric excess was determined by HPLC with a Chiralcel OJ column (95:5 hexanes/2-propanol; 1.0 mL/min): (*R*) enantiomer t_r = 30.1 min; (*S*) enantiomer t_r = 32.0 min; 98% ee. The analytical data obtained for this material were identical in all respects to those obtained for the decarboxylation product of (3*S*,5*S*)-methyl 6-benzyloxy-3,5-dihydroxyhexanoate (see Supporting Information). Thus, the acetone enolsilane adduct possesses an (*S*) configuration: $[\alpha]^{rt}_D$ −13.8 (*c* 0.58, CH_2Cl_2); IR (CH_2Cl_2) 3678, 3572, 3031, 2925, 2862, 1710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 5H), 4.57 (d, J = 12.2 Hz, 1H), 4.54 (d, J = 12.2 Hz, 1H), 4.26 (quintet, J = 5.6 Hz, 1H), 3.49 (dd, J = 4.6, 9.6 Hz, 1H), 3.44 (dd, J = 6.0, 9.6 Hz, 1H), 2.99 (br s, 1H), 2.69 (dd, J = 7.3, 17.0 Hz, 1H), 2.63 (dd, J = 4.4, 17.1 Hz, 1H), 2.18 (s, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.6, 137.8, 128.4, 127.8, 127.7, 73.4, 73.1, 66.8, 46.6, 30.8; LRMS (EI) *m*/*z* 208 M^+; HRMS (EI) exact mass calcd for $(C_{12}H_{16}O_3)^+$ requires *m*/*z* 208.1099, found *m*/*z* 208.1109.

Preparation of (*S*)-4-Benzyloxy-3-hydroxy-1-phenylbutan-1-one (Table 6, Entry 2). This compound was prepared according to the

general procedure employing [Cu(Ph-pybox)]$(SbF_6)_2$ (4.0 mL, 0.10 mmol, 100 mol %), except that less benzyloxyacetaldehyde (14 μL, 0.10 mmol) and the enolsilane of acetophenone (20 μL, 0.11 mmol) were used. The pure product was obtained as a white crystalline solid in 80% yield (21 mg, 80 μmol) after flash chromatography with 20% EtOAc/hexanes. Enantiomeric excess was determined by HPLC with a Chiralcel AS column (90:10 hexanes/2-propanol; 1.0 mL/min): (*S*) enantiomer t_r = 13.1 min; (*R*) enantiomer t_r = 33.9 min; 94% ee; mp 46.5−47.0 °C; $[\alpha]^{rt}_D$ −21.4 (*c* 0.46, CH_2Cl_2); IR (CH_2Cl_2) 3668, 3583, 3021, 2904, 2862, 1678 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (dt, *J* = 8.3, 1.4 Hz, 2H), 7.59 (tt, *J* = 1.4, 7.4 Hz, 1H), 7.47 (dt, *J* = 1.6, 7.6 Hz, 2H), 7.34 (m, 5H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.46 (app sextet, *J* = 5.2 Hz, 1H), 3.61 (dd, *J* = 4.9, 9.7 Hz, 1H), 3.57 (dd, *J* = 5.8, 9.7 Hz, 1H), 3.21 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 137.9, 136.7, 133.5, 128.6, 128.4, 128.1, 127.8 (2), 73.4, 73.2, 67.1, 41.8; LRMS (EI) *m*/*z* 270 M^+; HRMS (EI) exact mass calcd for $(C_{17}H_{18}O_3)^+$ requires *m*/*z* 270.1256, found *m*/*z* 270.1246.

Preparation of (2*S*,3*S*)-1-Benzyloxy-3,5-dimethyl-2-hydroxy-4-oxohexane (Table 6, Entry 3). This compound was prepared according to the general procedure employing [Cu(Ph-pybox)]$(SbF_6)_2$ (3.0 mL, 0.05 mmol, 10 mol %) and the enolsilane of 2-methyl-3-pentanone as a 90:10 mixture of *E*:*Z* isomers (132 μL, 0.60 mmol) to provide the pure product as a clear oil in 90% yield (113 mg, 0.45 mmol) after flash chromatography with 5−10% EtOAc/CH_2Cl_2 . Product ratios were determined by HPLC with a Chiralcel OD-H column (99:1 hexanes/2-propanol; 1.0 mL/min): anti enantiomers t_r = 18.4, 22.4 min; *syn*-(2*S*,3*S*) t_r = 19.4 min; *syn*-(2*R*,3*R*) t_r = 23.8 min; 95:5 syn:anti, 90% syn ee; $[\alpha]^{rt}_D$ +11.93 (*c* 2.3, CH_2Cl_2). Syn isomer: IR (CH_2Cl_2) 3686, 3577, 3065, 2974, 2875, 1705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H), 4.52 (s, 2H), 4.02 (dt, *J* = 4.8, 5.8 Hz, 1H), 3.47 (dd, *J* = 4.7, 9.6 Hz, 1H), 3.41 (dd, *J* = 6.2, 9.5 Hz, 1H), 2.96 (dq, *J* = 5.7, 7.2 Hz, 1H), 2.75 (septet, *J* = 6.9, 1H), 2.50 (br s, 1H), 1.14 (d, *J* = 7.2, 3H), 1.08 (d, *J* = 6.9, 3H), 1.05 (d, *J* = 6.9, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.4, 137.8, 128.4, 127.8 (2), 73.4, 71.6, 70.8, 45.9, 40.2, 18.1, 17.9, 12.0; LRMS (CI/NH_3) *m*/*z* 251 $(MH)^+$, 268 $(M + NH_4)^+$; HRMS (CI/NH_3) exact mass calcd for $(C_{15}H_{22}O_3 + NH_4)^+$ requires *m*/*z* 268.1913, found *m*/*z* 268.1920. Anti isomer: IR (CH_2Cl_2) 3687, 3579, 3054, 2974, 2877, 1711, 1604 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H), 4.57 (d, *J* = 11.9, 1H), 4.51 (d, *J* = 11.9, 1H), 3.87 (dt, *J* = 6.2, 5.2 Hz, 1H), 3.50 (d, *J* = 5.1 Hz, 2H), 3.05 (br s, 1H), 3.02 (dq, *J* = 6.7, 7.2 Hz, 1H), 2.73 (septet, *J* = 6.9, 1H), 1.10 (d, *J* = 7.2, 3H), 1.09 (d, *J* = 6.9, 3H), 1.06 (d, *J* = 6.9, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.1, 137.8, 128.4, 127.8 (2), 73.5, 72.9, 72.2, 45.7, 41.0, 17.8 (2), 14.2; LRMS (CI/NH_3) *m*/*z* 251 $(MH)^+$, 268 $(M + NH_4)^+$; HRMS (CI/NH_3) exact mass calcd for $(C_{15}H_{22}O_3 + NH_4)^+$ requires *m*/*z* 268.1913, found *m*/*z* 268.1919.

Preparation of (1′*S*,2*S*)-2-(2′-Benzyloxy-1′-hydroxyethyl)cyclopentan-1-one (Table 6, Entry 5). This compound was prepared according to the general procedure employing [Cu(Ph-pybox)]$(SbF_6)_2$ (3.0 mL, 0.05 mmol, 10 mol %) and the enolsilane derived from cyclopentanone (107 μL, 0.60 mmol) to provide the pure product as a white powder in 90% yield (105 mg, 0.45 mmol) after flash chromatography with 30−40% EtOAc/hexanes. Product ratios were determined by HPLC with a Chiralcel AD column (95:5 hexanes/2-propanol; 1.0 mL/min): anti enantiomers t_r = 17.1, 18.9 min; *syn*-(1′*R*,2*R*) t_r = 20.4 min; *syn*-(1′*S*,2*S*) t_r = 23.3 min; 95:5 syn:anti; 96% syn ee; $[\alpha]^{rt}_D$ −82.0 (*c* 4.6, CH_2Cl_2). Syn isomer: $[\alpha]^{rt}_D$ −90.5 (*c* 1.3, $CHCl_3$); >99:1 syn:anti; 96% syn ee; mp 53−55 °C (white powder, racemic); IR (CH_2Cl_2) 3682, 3600, 3057, 2964, 2882, 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H, Ph), 4.56 (d, *J* = 12.1 Hz, 1H), 4.52 (d, *J* = 12.1 Hz, 1H), 4.25 (m, 1H), 3.54 (dd, *J* = 4.2, 9.7 Hz, 1H), 3.49 (dd, *J* = 7.2, 9.6 Hz, 1H), 2.83 (br s, 1H), 2.28 (ddd, *J* = 1.3, 8.0, 17.9 Hz, 1H), 2.21 (dddd, *J* = 1.0, 3.9, 8.3, 10.7 Hz, 1H), 2.13 (ddd, *J* = 8.5, 10.7, 18.5 Hz, 1H), 2.04 (m, 2H), 1.96 (m, 1H), 1.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 222.0, 137.8, 128.4, 127.7, 127.6, 73.3, 72.6, 68.8, 51.1, 38.7, 23.7, 20.7; LRMS (EI) *m*/*z* 234 M^+; HRMS (EI) exact mass calcd for $(C_{14}H_{18}O_3)^+$ requires *m*/*z* 234.1256, found *m*/*z* 234.1273.

Preparation of (*R*)-*tert*-Butyl 4-Benzyloxy-3-hydroxybutanethioate Using [Cu(*tert*-Bu-box)](OTf)$_2$ as the Catalyst (7, Table 7, Entry 1) (General Procedure for [Cu(*tert*-Bu-box)](OTf)$_2$ in the Benzyloxyacetaldehyde Aldol Reactions). To a −78 °C solution of [Cu(*tert*-Bu-box)]$(OTf)_2$ (0.05 mmol, 10 mol %) in CH_2Cl_2 (2 mL) was added benzyloxyacetaldehyde (70.0 μL, 0.50 mmol) followed by the silylketene acetal of *tert*-butyl thioacetate (122 mg, 0.60 mmol, 153 μL). The resulting solution was stirred at −78 °C until the aldehyde was completely consumed (1 h), as determined by TLC (30% EtOAc/hexanes). The reaction mixture was then filtered through a 1.5- × 8-cm plug of silica gel with Et_2O (50 mL). Concentration of the ether solution gave a clear oil, which was dissolved in THF (10 mL) and 1 N HCl (2 mL). After standing at room temperature for 15 min, this solution was poured into a separatory funnel and diluted with Et_2O (10 mL) and H_2O (10 mL). After mixing, the aqueous layer was discarded, and the ether layer was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The resulting ether layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by flash chromatography with 20% EtOAc/hexanes provided the pure (*R*)-hydroxy ester. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (94.2:0.8:5.0 hexanes/2-propanol/EtOAc; 1.0 mL/min): (*R*) enantiomer t_r = 16.3 min; (*S*) enantiomer t_r = 17.9 min; 91% ee. The analytical data obtained from this material (^1H NMR, ^{13}C NMR, and HRMS) were identical to those described above, with the exception of the optical rotation, which was of the opposite sign: $[\alpha]^{rt}_D$ +10.4 (*c* 2.9, CH_2Cl_2).

Other aldehyde aldol reactions with the [Cu(*tert*-Bu-box)]$(OTf)_2$ catalyst were performed analogously using the indicated silylketene acetal and aldehyde.

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Supporting Information Available: General experimental information; absolute and relative stereochemical proofs; minor diastereomer characterization date; nonlinear effects experiments; silyl crossover experiments; double stereodifferentiating experiments; EPR spectra; ESI data; and X-ray crystallogrpahic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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