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

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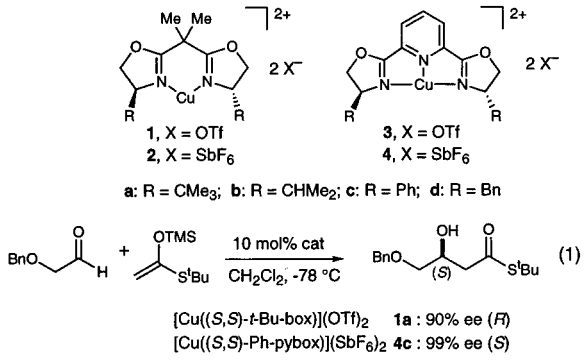
Abstract: The C_2-symmetric (*S,S*)-*tert*-butyl-bis(oxazolinyl)Cu(OTf)$_2$ complex (**1a**) has been shown to catalyze the enantioselective aldol reaction between α-keto esters and silylketene acetals or enolsilanes with enantioselectivities ranging from 93 to 99%. With substituted silylketene acetals, syn reaction diastereoselection ranging from 90:10 to 98:2 and enantioselectivities ranging from 93 to 98% are observed. High levels of carbonyl regioselectivity (98:2), diastereoselectivity (93:7), and enantioselectivity (97% ee) are also observed in the aldol addition to 2,3-pentanedione. In all instances, the aldol adducts are generated in high yield and in excellent enantiomeric excess using as little as 1 mol % of the chiral complex **1a**. Mechanistic insight into the pyruvate aldol reaction has also been gained. Silyl crossover experiments demonstrate that the silyl-transfer step is intermolecular. Based upon these results, TMSOTf has been identified as an addend to accelerate these reactions. Furthermore, solvent was shown to have a dramatic impact on the rates of addition and catalyst turnover in the pyruvate aldol reaction. Crystallographic structures and semiempirical calculations provide insight into the mode of asymmetric induction, allowing the construction of a model in which chelation of the pyruvate ester through a square planar Cu(II) complex accounts for the observed sense of asymmetric induction. Two other Cu(II) complexes, [Cu((*S,S*-*i*-Pr-pybox)](SbF$_6$)$_2$ and bis(imine) complex **26**, have also been evaluated as enantioselective catalysts for the pyruvate aldol reaction; however, the scope of the process with these systems is more limited.

Introduction

Previous work from our laboratory has demonstrated that bidentate bis(oxazolinyl) (box)−and tridentate bis(oxazolinyl)-pyridine (pybox)−Cu(II) complexes **1**−**4** can function as effective chiral Lewis acid catalysts in the Diels−Alder,[1] aldol,[2] hetero-Diels−Alder,[3] and carbonyl-ene reactions[4] with substrates that can participate in catalyst chelation. In the preceding article,[2b] we have reported a study employing both the *tert*-butyl-box (**1a**) and phenyl-pybox (**4c**) Cu(II) complexes (Scheme 1) as enantioselective Lewis acid catalysts for the aldol reactions of (benzyloxy)acetaldehyde with a broad range of enolsilanes (eq 1). The success of (benzyloxy)acetaldehyde in the Cu(II)-catalyzed aldol reaction emanates from the ability of this substrate to engage in chelate-organized association with the Lewis acidic Cu(II) center, resulting in excellent carbonyl π-facial discrimination in the derived aldol reactions. Based on this precedent, an investigation into the extension of these chiral complexes to the aldol reactions of pyruvate esters was undertaken. Should this family of carbonyl substrates also meet the chelation criterion, the derived substrate−catalyst complexes **A** and **B** should also afford highly enantioselective aldol bond constructions (eq 2). This process is an attractive target for enantioselective catalysis since it would provide access to the production of chiral tertiary alcohols, moieties present in numerous natural products.[5] In addition, the resultant substituted succinate products are valuable synthons in pharmaceutical synthesis.[6] In particular, this class of molecules has emerged

Scheme 1



(1) Reference 2b, footnote 6.

(2) (a) Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814−5815. (b) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Connell, B. T. *J. Am. Chem. Soc.* **1999**, *121*, 669−685.

(3) Reference 2b, footnote 7a.

(4) Reference 2b, footnote 7b.

(5) Representative examples: (a) Cinatrin C: Itzaki, H.; Nagashima, K.; Matsumoto, K.; Nakai, H.; Terui, Y. *J. Antibiot.* **1992**, *45*, 38−49. (b) Integerrimine: Robins, D. J. *Forschr. Chem. Org. Naturst.* **1982**, *41*, 115. (c) Harringtonine: Takano, I.; Yasuda, I.; Nishijima, M.; Hitotsuyanagi, Y.; Takeya, K.; Itokawa, H. *Phytochemistry* **1997**, *44*, 735 and references therein. (d) K252a: Wood, J. L.; Stoltz, B. M.; Dietrich, H.-J. *J. Am. Chem Soc.* **1995**, *117*, 10413−10414 and references therein. (e) Fostriecin: Boger, D. L.; Hikota, M.; Lewis, B. M. *J. Org. Chem.* **1997**, *62*, 1748−1753 and references therein. (f) Viridiofungin: Harris, G. H.; Jones, E. T. T.; Meinz, M. S.; Nallin-Omstead, M.; Helms, G. L.; Bills, G. F.; Zink, D.; Wilson, K. E. *Tetrahedron Lett.* **1993**, *34*, 5235−5238. (g) Erythromicin: McGuire, J. M.; Bunch, R. L.; Anderson, R. C.; Boaz, H. E.; Flynn, E. H.; Powell, H. M.; Smith, J. W. *Antibiot. Chemother.* **1952**, *2*, 281−283. (h) Zaragozic acid: Wilson, K. E.; Burk, R. M.; Biftu, T.; Ball, R. G.; Hoogsteen, K. *J. Org. Chem.* **1992**, *57*, 7151−7158.

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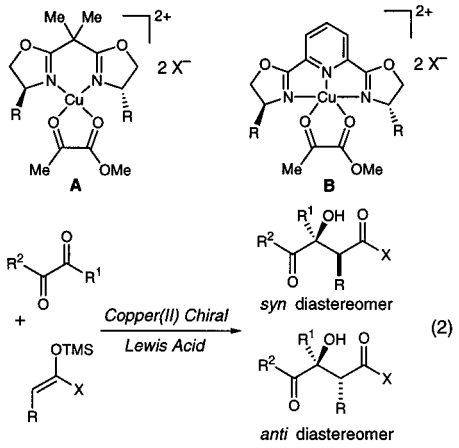
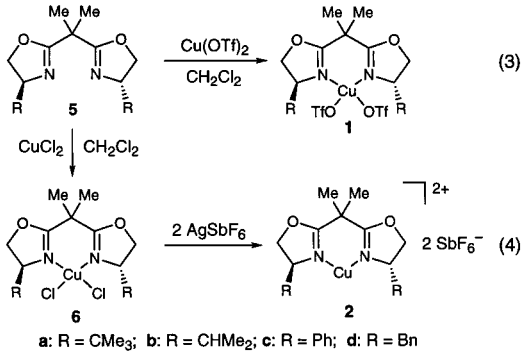


as effective peptide isosteres for incorporation into matrix metalloproteinase (MMP) inhibitors, compounds that are currently enjoying use in therapeutic areas ranging from arthritis to cancer.[7] Although excellent stereocontrol in these reactions may be achieved through the use of stoichiometric chiral ester controllers and chiral metal complexes,[8] to our knowledge this is the first report of a catalytic enantioselective addition of enolsilanes to pyruvate esters. In this investigation, we document the mechanism and scope of the enantioselective Cu(II)-catalyzed pyruvate aldol process (eq 2).[9]

Preliminary Results

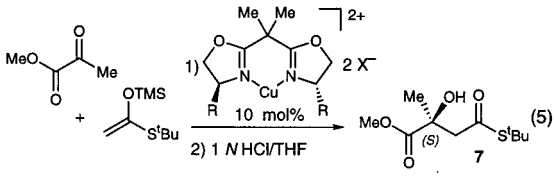
Bis(oxazoline) Ligand Survey. The bis(oxazolinyl) copper complexes **1** and **2** were initially evaluated for their ability to catalyze the addition of a representative enolsilane to methyl pyruvate. The bis(oxazolinyl) copper complexes **1a**−**d** were prepared by stirring a solution of the bis(oxazoline) ligand **5**[10] and $Cu(OTf)_2$ (typically 10 mol %, ∼0.03 M in catalyst) in CH_2Cl_2, (25 °C, 3 h) as previously described (eq 3).[9] The cationic hexafluoroantimonate complex **2a** was formed by halide abstraction from the preformed [Cu(*t*-Bu-box)]Cl_2 complex **6a**[10] with $AgSbF_6$, followed by filtration through dry Celite (or a PTFE 0.45-μm filter) to remove the precipitated AgCl (eq 4).

Addition of methyl pyruvate to a cooled solution (CH_2Cl_2, −78 °C) of the catalyst, followed by subsequent dropwise addition of the trimethylsilylketene acetal of *tert*-butyl thioacetate,[11] afforded the silyl-protected β-hydroxy ester. Brief



treatment of this silyl ether with 1 N HCl in THF produced the required alcohol **7** (eq 5), the enantioselectivity of which was assayed by chiral HPLC (Daicel OD-H column). The absolute configuration of the methyl pyruvate adduct was secured by conversion to dimethyl citramalate and comparison of the optical rotation to the literature value.[12] Several [Cu((*S*,*S*)-box)]$(OTf)_2$ complexes (**1a**−**d**, 10 mol %) were screened in the addition of *tert*-butyl thioacetate trimethylsilylketene acetal to methyl pyruvate (eq 5, Table 1, entries 1−4). All of the reactions proceeded to full conversion within 2 h at −78 °C. Variation of the ligand substituent (R, eq 5) revealed that only the *tert*-butyl box-derived copper catalyst, [Cu((*S*,*S*)-*t*-Bu-box)]$(OTf)_2$ (**1a**), yielded a highly enantioselective process, affording the (*S*) tertiary alcohol product **7** in 98% ee (Table 1, entry 4). Use of the corresponding [Cu((*S*,*S*)-*t*-Bu-box)]$(SbF_6)_2$ (**2a**) as a catalyst in this reaction revealed the expected rate enhancement;[1] however, the product was produced in only 75% ee (Table 1, entry 5). Accordingly, the [Cu((*S*,*S*)-*t*-Bu-box)]$(OTf)_2$ catalyst **1a** was selected as the optimal complex derived from the box ligand family.

Table 1. Effect of Ligand and Counterion in the Catalyzed Pyruvate Aldol Reaction (eq 5)[a]



entry	R	X	time	% ee[b]
1	Ph (**1c**)	OTf	1.5 h	43
2	Bn (**1d**)	OTf	3 h	10
3	$CHMe_2$ (**1b**)	OTf	1.5 h	23
4	CMe_3 (**1a**)	OTf	2 h	98
5	CMe_3 (**2a**)	SbF_6	0.5 h	75

[a] All reactions were carried out in CH_2Cl_2 (0.2 M in substrate) at -78 °C and proceeded to complete conversion. [b] Enantiomeric excess determined by HPLC using a Chiralcel OD-H column.

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 6). 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

(6) (a) Babine, R. E.; Bender, S. L. *Chem. Rev.* **1992**, *97*, 1359−1472. Substituted succinates as applied to collagenase inhibitors: Schwartz, M. A.; Van Wart, H. E. *Prog. Med. Chem.* **1992**, *29*, 271−334.

(7) (a) Davidson, A. H.; Drummond, A. H.; Galloway, W. A.; Whittaker, M. *Chem. Ind.* **1997**, 258−261. (b) Levy, D. E.; Lapierre, F.; Liang, W.; Ye, W.; Lange, C. W.; Li, X.; Grobelny, D.; Casabonne, M.; Tyrell, D.; Holme, K.; Nadzan, A.; Galardy, R. E. *J. Med. Chem.* **1998**, *41*, 199−223 and references therein.

(8) Diastereoselective pyruvate aldol additions: (a) Jacobson, I. C.; Reddy, G. P. *Tetrahedron Lett.* **1996**, *37*, 8263−8266. (b) Akiyama, T.; Ishikawa, K.; Ozaki, S. *Synlett* **1994**, 275−276. (c) Chen, M.-Y.; Fang, J.-M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1737−1741. (d) Ojima, I.; Yoshida, K.; Inaba, S. *Chem. Lett.* **1977**, 429−432. Stoichiometric chiral metal−complex promoted: (e) Kobayashi, S.; Horibe, M.; Saito, Y. *Tetrahedron* **1994**, *50*, 9629−9642. (f) Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1992**, *57*, 1324−1326. (g) Kobayashi, S.; Fujishita, Y.; Mukaiyama, T. *Chem. Lett.* **1989**, 2069−2072. One catalyzed aldol addition to pyruvate esters has been reported, but it is limited to isocyanoacetate or isocyanoacetamide nucleophiles: Ito, Y.; Sawasura, M.; Hamashima, H.; Emura, T.; Hayashi, T. *Tetrahedron Lett.* **1989**, *30*, 4681−4684.

(9) A preliminary account of this work has appeared: Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem Soc.* **1997**, *119*, 7893−7894.

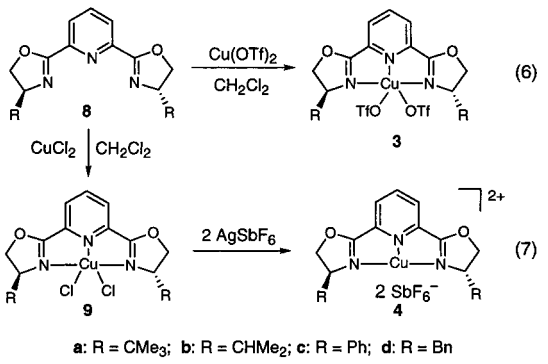
(10) Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541−4544 and references therein.

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

(12) Stevens, R. W.; Mukaiyama, T. *Chem. Lett.* **1983**, 1799−1802.

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

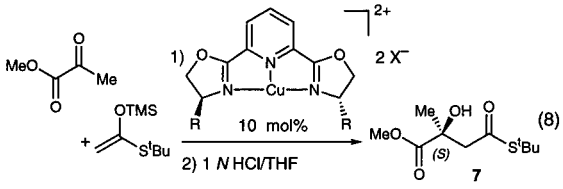
abstraction with $AgSbF_6$ and filtration[14] to remove the precipitated AgCl (eq 7).



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

Investigation into the utility of the [Cu((*S*,*S*)-pybox)]$(SbF_6)_2$ complex **4** demonstrated that these complexes are also effective catalysts for the pyruvate aldol reaction (eq 8). Variation of the ligand substituent (R, eq 8) and counterion (X, eq 8) revealed that [Cu((*S*,*S*)-*i*-Pr-pybox)]$(SbF_6)_2$ complex (**4b**) was the optimal catalyst in this series, affording the (*S*) tertiary alcohol product **7** in 95% ee and 92% yield (Table 2, entry 4). The corresponding triflate complexes were inferior catalysts for this reaction; for example, [Cu((*S*,*S*)-*i*-Pr-pybox)]$(OTf)_2$ (**3b**) necessitated the use of a higher reaction temperature (−20 °C) and afforded the product in lower enantioselectivity (entry 5, 61% ee).

Table 2. Effect of Ligand and Counterion in the Catalyzed Pyruvate Aldol Reaction (eq 8)[a]



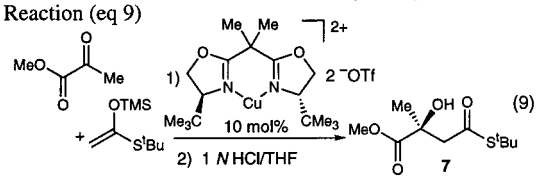
entry	R	X	time, (T)	% ee[b]
1	CMe_3 (**4a**)	SbF_6	30 min (-50 °C)	4
2	Ph (**4c**)	SbF_6	15 min (-78 °C)	62
3	Bn (**4d**)	SbF_6	15 min (-78 °C)	79
4	$CHMe_2$ (**4b**)	SbF_6	15 min (-78 °C)	95[c]
5	$CHMe_2$ (**3b**)	OTf	24 h (-20 °C)	61[d]

[a]All reactions were carried out in CH_2Cl_2 (0.2 M in substrate) and proceeded to complete conversion. [b]Enantiomeric excess determined by HPLC using a Chiralcel OD-H. [c]92% isolated yield after chromatography. [c]68% isolated yield after chromatography.

Reaction Optimization. Due to the superior enantioselectivity exhibited by the [Cu((*S*,*S*)-*t*-Bu-box)]$(OTf)_2$ complex (**1a**) (Table 1, entry 4), a study was initiated to explore the pyruvate aldol reaction parameters with this catalyst system.

Reaction Solvents. Solutions of the [Cu((*S*,*S*)-*t*-Bu-box)]-$(OTf)_2$ complex (**1a**) in representative solvents were generated using the standard procedure. With the lone exception of hexane, the complex was readily soluble in the indicated solvents. The solvent survey (Table 3, eq 9) revealed that THF was the optimal solvent for this transformation, providing the aldol adduct rapidly (1 h) and in high enantioselectivity (99% ee). The product was also formed in high enantioselectivity in Et_2O (99% ee), but reaction times were extended (12 h) compared to those in THF (1 h). As previously demonstrated (Table 1), dichloromethane was also an excellent solvent for the pyruvate aldol reaction (2 h, 98% ee). Although the high melting point of dioxane precluded a direct comparison, results obtained at room temperature (92% ee, 10 min) compared favorably with those observed in THF (20 °C, 92% ee, <15 min). Solvents such as nitromethane and acetonitrile were found to be the least effective in terms of enantioselectivity ($MeNO_2$: 75% ee; MeCN: 23% ee).

Table 3. Effect of Solvent in the Catalyzed Pyruvate Aldol Reaction (eq 9)



solvent	T	time	% ee	% yield
THF	-78 °C	1 h	99	95
Et_2O	-78 °C	12 h	99	94
CH_2Cl_2	-78 °C	2 h	98	93
$PhCH_3$	-20 °C	3 h	96	91
Hexane[a]	-20 °C	3 d	96	42
$PhCF_3$	-20 °C	20 h	95	88
Dioxane	+20 °C	10 min	92	84
CH_3NO_2	-20 °C	15 min	75	95
CH_3CN	-40 °C	2 h	23[b]	ND[c]

[a]The catalyst was not soluble in this solvent. [b](*R*) absolute configuration. [c]The yield was not determined but the reaction proceeded to complete conversion.

Catalyst Properties. Our prior studies in the [Cu((*S*,*S*)-*t*-Bu-box)]$(OTf)_2$ (**1a**)-catalyzed Diels−Alder cycloaddition reaction have shown that a minimum complexation time of 2 h is required for the formation of the catalyst in CH_2Cl_2. In the present investigation, complexation of *t*-Bu-box and $Cu(OTf)_2$ in THF results in a clear green homogeneous catalyst solution (**1a**) within 10 min. No difference in catalytic efficiency or selectivity was observed with complexation times ranging from 15 min to 4 h (99% ee, >95% yield, 1 h); however, a slight erosion in catalytic activity was observed when a 12-h complexation time was used (2 h, 99% ee). Typically, a complexation time of 1 h was employed for the aldol studies conducted in THF.[15]

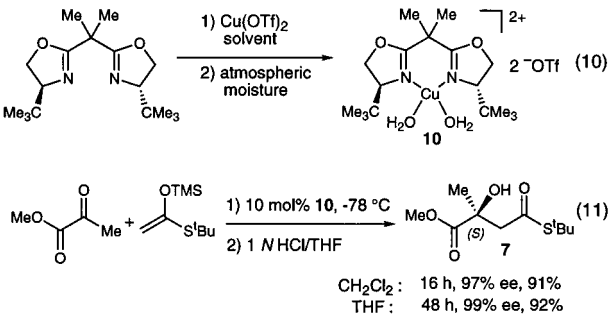
The erosion of catalytic activity observed with extended complexation times is likely due to catalyst hydration, which is visually evident in the color change of the catalyst solution from the characteristic green for the anhydrous complex to blue for its hydrated counterpart. Support for this hypothesis was obtained when a freshly prepared solution (THF or CH_2Cl_2) of [Cu(*t*-Bu-box)]$(OTf)_2$ was exposed to the atmosphere, resulting in the immediate formation of a blue solution (eq 10). Concentration in vacuo yielded pale blue crystals, the structure of which was confirmed by X-ray crystallographic analysis to be the bis(hydrate) [Cu((*S*,*S*)-*t*-Bu-box)$(H_2O)_2$]$(OTf)_2$ complex (**10**).[16] Employment of complex **10** in the pyruvate aldol reaction (eq 11) revealed that the bis(hydrate) was a less efficient catalyst than its anhydro counterpart (CH_2Cl_2: 16 h, 97% ee vs 2 h, 98% ee; THF, 48 h, 99% ee vs 1 h, 99% ee); however, complete catalytic activity could be restored by stirring the bis(hydrate) with powdered 3-Å molecular sieves for 1 h prior to commenc-

(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.

(15) A 3-h complexation time was utilized in this study for the reactions performed in CH_2Cl_2.

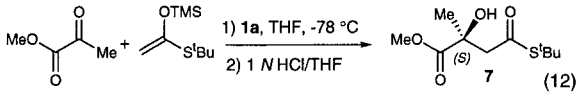
(16) The X-ray structure of **10** has recently been published: Evans, D. A.; Olhava, E. J.; Johnson, J. S.; Janey, J. M. *Angew. Chem.* **1998**, *24*, 3554−3557.

ing the reaction.[17] This observation has been noted elsewhere in a catalyzed hetero Diels−Alder reaction.[16]



The effect of catalyst loading on the [Cu((*S*,*S*)-*t*-Bu-box)]-$(OTf)_2$-catalyzed pyruvate aldol reaction in THF (eq 12) was also examined (Table 4). These experiments illustrate that excellent levels of enantioselection are maintained when employing catalyst loading levels as low as 1 mol % (Table 4, 10 mol %, 1 h, 99% ee; 1 mol %, 2 h, 99% ee). In contrast, the lowest catalyst loading that could be implemented in CH_2Cl_2 was 2 mol % (1.70 M, 14 h, 97% ee).

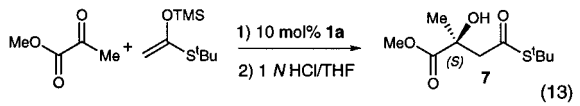
Table 4. Effect of Catalyst Loading in the Catalyzed Pyruvate Aldol Reaction (eq 12)



mol% **1a**	$[pyruvate]_0$	time	% ee	% yield
10	0.3 M	1 h	99	100
5	0.5 M	1 h	99	96
2	1.0 M	1 h	99	92
1	1.5 M	2 h	99	95

Temperature Profile. A temperature profile of the pyruvate aldol reaction (eq 13) in both CH_2Cl_2 and THF demonstrated that this reaction performed exceptionally well over a wide temperature range (Table 5). Remarkably, only a 7% drop in enantioselection was observed in THF over a 100-deg temperature range (−78 → +20 °C, 99% → 92% ee); a similar favorable trend was also observed in CH_2Cl_2 (−78 → +20 °C, 98 → 85% ee).[18]

Table 5. Temperature Profile of the Catalyzed Pyruvate Aldol Reaction (eq 13)[a]

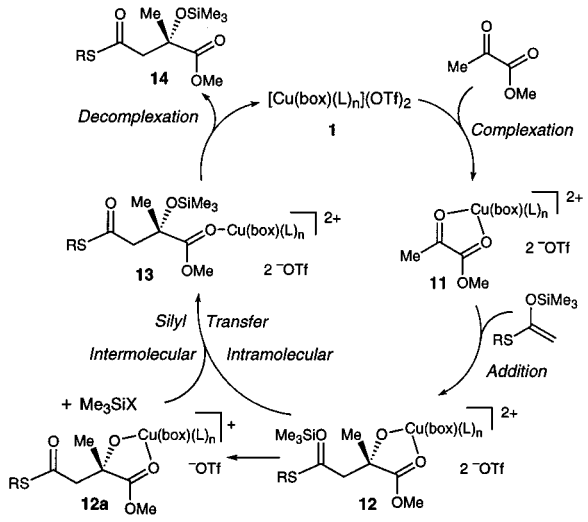


T (°C)	% ee (CH_2Cl_2)	% ee (THF)
-78	98	99
-50	95	97
-20	92	95
+20	85	92

[a] All reactions were 0.3 M in substrate and proceeded to completion

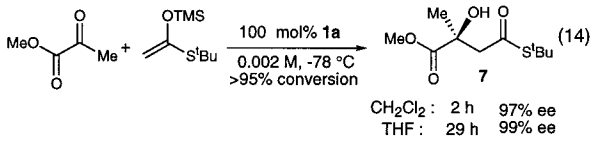
Reaction Mechanism. The proposed catalytic cycle for the [Cu((*S*,*S*)-*t*-Bu-box)](OTf)$_2$-catalyzed pyruvate aldol reaction is outlined in Scheme 2. Chelation of methyl pyruvate to the Cu-

Scheme 2



(II) center produces the activated substrate−catalyst complex **11**, which undergoes nucleophilic addition to afford the Cu-aldolate **12**. Silylation to form **13** and subsequent decomplexation delivers the product **14** and concomitantly regenerates the catalyst **1a**.

Role of Solvent on the Relative Rates of Addition. The rate increase encountered in THF (Table 3) is counterintuitive since it was anticipated that this donor solvent would buffer the Lewis acidity of the metal center (**1**, L = THF, Scheme 2). Accordingly, experiments were designed to probe the origin of this observation. First, to determine if the rate of nucleophilic addition (**1** → **11** → **12**), rather than catalyst turnover (**12** → **13** → **14**, Scheme 2), was dependent on solvent, reactions were performed using stoichiometric catalyst (**1a**). To obtain observable rates, highly dilute conditions consisting of 0.10 mmol of pyruvate in 50 mL of solvent (0.002 M) were employed. When the reactions were monitored at −78 °C by GLC, methyl pyruvate was completely consumed within 29 h in THF and 2 h in CH_2Cl_2 (eq 14). As the silyl ether adduct was not observed



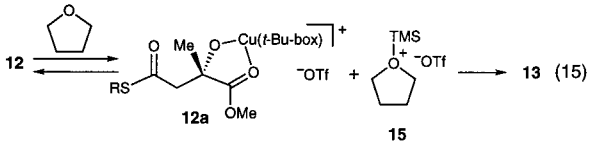
in these reactions, the product alcohols were analyzed directly by chiral HPLC (CH_2Cl_2, 97% ee; THF, 99% ee). Since similar levels of enantioselection were observed at both stoichiometric and substoichiometric (≤10 mol %) catalyst loadings, the fidelity of this catalyst system appears to be high.

The finding that the Mukaiyama aldol reaction employing stoichiometric amounts of [Cu(*t*-Bu-box)](OTf)$_2$ was faster in CH_2Cl_2 than in THF implies that the first two steps of the catalytic cycle (i.e., complexation and addition) proceed overall more rapidly in CH_2Cl_2. However, the same reaction using substoichiometric amounts (10 mol %) of the chiral Lewis acid proceeded faster in THF than in CH_2Cl_2 (Table 3). The steps composing catalyst turnover (i.e., silylation and decomplexation), therefore, must be faster in THF than in CH_2Cl_2. To rationalize these data, we propose that THF is associating with the metal center to effectively reduce the overall Lewis acidity of the copper complex (**1**, L = THF, Scheme 2). As a result, solvent (THF) association would cause the rate retardation observed in the initial steps: (1) complexation would be less

(17) Since the [Cu(*tert*-Bu-box)(H_2O)$_2$](OTf)$_2$ crystals can be stored indefinitely at room temperature without special precautions, the bishydrate provides a convenient source of readily activated catalyst.

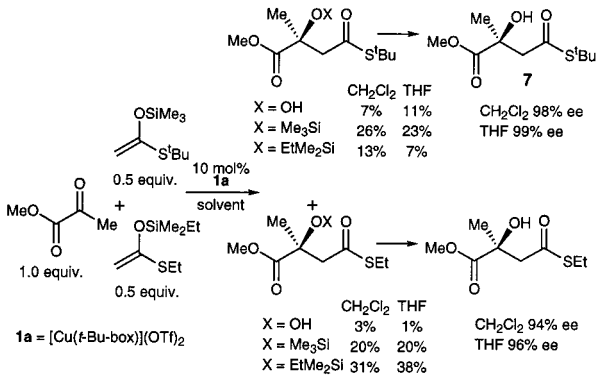
(18) Since this reaction is exothermic, it was necessary to add the silylketene acetal dropwise to maintain a constant internal temperature.

favorable and (2) nucleophilic addition would be slower due to the moderated Lewis acidity of the pyruvate−catalyst complex **11** (L = THF). Likewise, this rationale could explain the increased rate of catalyst turnover in THF since a less Lewis acidic metal center would (1) decrease the Cu−O bond strength in aldolate **12**, thereby resulting in a more facile silylation, and (2) favor product decomplexation. Alternatively, the high concentration of THF (i.e., the reaction solvent) may be accelerating catalyst turnover by reacting with **12** to form a more accessible silylating species **15** (eq 15). This silyl shuttle proposal would necessarily require that the silyl-transfer step be intermolecular (**12** → **12a** → **13**, Scheme 2), whereas silylation could be either intra- or intermolecular in the THF association mechanism (vide supra).



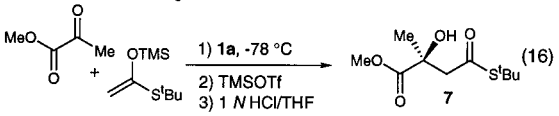
Silyl Crossover Experiments. It is evident from the preceding discussion that the silyl-transfer component of the catalytic cycle (Scheme 2) warranted investigation. Silylation of the Cu-aldolate intermediate may proceed via an intramolecular (**12** → **13**) or intermolecular (**12** → **12a** → **13**) process to furnish the observed product **14**. It has been reported that intermolecular silyl transfer results in a catalytically competent silicon intermediate (Me_3SiX), which affords an avenue for a competing *achiral* catalytic process.[19] The details of this silyl-transfer event were investigated in the present system, in both THF and CH_2Cl_2, by employing a mixture of two different silylketene acetals which should exhibit similar reactivities (Scheme 3).[20]

Scheme 3



Treatment of 0.5 equiv each of the depicted silylketene acetals with 1.0 equiv of methyl pyruvate and 10 mol % of [Cu(*t*-Bu-box)](OTf)$_2$ (**1a**) afforded significant quantities of the four possible products, as detected by GLC analysis. Deprotection of the silyl ethers and chiral HPLC analysis of the derived alcohols indicated that both aldol adducts were formed in high enantiomeric excess. Accordingly, it appears that, although there is a large intermolecular silyl-transfer component in this aldol reaction, the transient silyl species (Me_3SiX)[21] does not compete effectively at −78 °C with the *cationic* copper catalyst in aldol catalysis. Control experiments indicated that neither the silylketene acetals nor the silyl ether products were subject to silyl exchange initiated by the catalyst, thereby verifying that silyl crossover occurs during the course of the reaction.

Table 6. Effect of TMSOTf in the Catalyzed Pyruvate Aldol Reaction (eq 16)



solvent	mol% **1a**	mol% TMSOTf	time	% ee
CH_2Cl_2	0	100	NR	--
CH_2Cl_2	2	0	14 h	97
CH_2Cl_2	2	100	0.5 h	97
THF	1	0	12 h	99
THF	1	90	3 h	99

Accelerating Effect of TMSOTf. The results from the silyl crossover experiments incontrovertibly determined that the silyl-transfer process is intermolecular (**12a** → **13**, Scheme 2). Consequently, if this event is also the rate-limiting step,[22] an increase in the concentration of silylating species would produce an increase in the overall reaction rate. Addition of an exogenous silylating source, such as TMSOTf, to the reaction mixture could effect this proposed rate acceleration; however, this species itself could potentially serve as a racemic catalyst.[19] Despite the ample precedent that TMSOTf is an effective catalyst for the aldol reaction,[23] control experiments revealed that 1 equiv of this Lewis acid did not promote the reaction of methyl pyruvate and *tert*-butyl thioacetate silylketene acetal after 2.5 h at −78 °C (Table 6).[24] When the pyruvate aldol reaction was conducted exclusively in the presence of 2 mol % of the [Cu(*t*-Bu-box)](OTf)$_2$ catalyst (**1a**), the reaction required 14 h to reach completion (97% ee). In contrast, the same reaction performed with *both* 2 mol % of the [Cu((*S*,*S*)-*t*-Bu-box)](OTf)$_2$ (**1a**) *and* 100 mol % TMSOTf afforded the aldol adduct within 35 min (97% ee, Table 6); most significantly, no decline in enantioselectivity was observed upon utilization of this achiral Lewis acid.

The decision to add TMSOTf to the Cu(II)-catalyzed pyruvate aldol reactions conducted in CH_2Cl_2 was based upon the hypothesis that silyl transfer was the rate-limiting step in this process. When TMSOTf was added to the same reaction in THF, the reaction was also accelerated, but not to the same extent as in CH_2Cl_2. For example, at the 1 mol % catalyst level, addition of 0.9 equiv of TMSOTf resulted in only a 4-fold rate increase (Table 6), as compared to the 24-fold enhancement in CH_2Cl_2. This rate acceleration effect, resulting from the unique, synergistic relationship between an achiral (TMSOTf) and chiral Lewis acid **1a**, would prove to be extremely useful for reactions involving hindered substrates, which would not proceed to completion without addition of TMSOTf (see Reaction Scope).

The above results indicate that both THF and TMSOTf accelerate the Cu(II)-catalyzed pyruvate aldol reaction by facilitating catalyst turnover and, therefore, will only be beneficial if the addition step occurs at a reasonable rate. This point was established when hindered silylketene acetal substrates derived from substituted propionates were employed in this

(19) (a) Hollis, T. K.; Bosnich, B. *J. Am. Chem. Soc.* **1995**, *117*, 7, 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.

(20) Mikami, K.; Matsukawa, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 4077−4078.

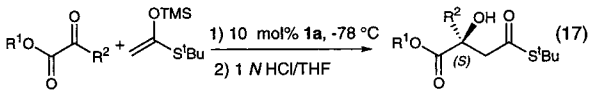
(21) Potental silylating sources include TMSOTf and intermediate **12**.

(22) During the course of our studies in CH_2Cl_2 the formation of the intermediate alcohol was initially detected, which was slowly converted to the silyl ether product.

(23) (a) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248. (b) Mukai, C.; Hashizume, S.; Nagami, K.; Hanaoka, M. *Chem. Pharm. Bull.* **1990**, *38*, 1509.

(24) The same reaction employing only the chiral Cu(II) catalyst was typically complete within this period.

Table 7. Catalyzed Enantioselective Aldol Reactions with Representative Pyruvate Esters (eq 17)



			CH_2Cl_2		THF	
entry	R^1	R^2	% ee[a]	% yield	% ee[a]	% yield
1	Me	Me	98[b]	92	99[b,d]	96
2	Bn	Me	98[b]	98	99[b]	95
3	^{t}Bu	Me	99[c]	80	99[c]	91
4	Me	Et	91[c]	86	94[c]	84
5	Me	^{i}Bu	75[c]	53	94[c,d]	94
6	Et	^{i}Pr	22[c]	90[e]	36[c]	36[f]

[a]Enantiomeric excess determined by HPLC using a Chiralcel OD-H or AD column. [b]Absolute configurations assigned by conversion to dimethyl citramalate (see supporting information). [c]Absolute configuration assigned by analogy. [d]The identical enantioselectivity and similar yields were obtained using 1 mol% (entry 1) or 2 mol% (entry 5) catalyst (<24 h, -78 °C). [e]Percent conversion. [f]Reaction temp -60 °C.

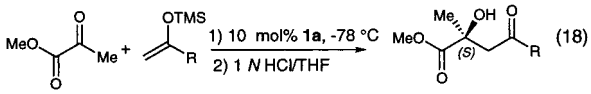
process (see Reaction Scope). Consequently, the optimal solvent for the pyruvate aldol reaction may vary depending on the specific substrates employed (vide infra).

Reaction Scope [Cu((*S,S*)-*t*-Bu-box)](OTf)$_2$ (1a). Throughout the investigation into the scope of the pyruvate aldol process catalyzed by **1a**, both THF and CH_2Cl_2 were evaluated as reaction solvents, and the results are compiled in the Tables 7−9. Those experiments that probe the scope of the α-keto ester reaction component with catalyst **1a** are summarized in Table 7. Excellent enantioselectivities were observed in the reactions of the silylketene acetal derived from *tert*-butyl thioacetate with methyl, benzyl, and *tert*-butyl pyruvate (entries 1−3, 98−99% ee), suggesting that the stereochemical course of this process is tolerant of the nature of the ester substituent (R^1, eq 17). When the acyl substituent of the pyruvate ester is varied ($R^2 \neq$ Me, eq 17), the advantage of THF over CH_2Cl_2 as the reaction solvent becomes evident. Good enantioselection (≥91% ee) was observed in both solvents when the acyl substituent R^2 is primary (Me, Et entries 1, 4); however, when R^2 was β-branched (R^2 = ^{i}Bu), only the reaction in THF afforded a highly enantioselective process (entry 5, CH_2Cl_2, 75% ee; THF, 94% ee). The limitation of this methodology was encountered with more sterically demanding α-branched substituents (entry 6, R^2 = ^{i}Pr, CH_2Cl_2, 22% ee; THF, 36% ee). Finally, the use of lower catalyst loadings is possible with acetate-derived silylketene acetals in THF, as the same enantioselectivity and yields were obtained when the reactions in entries 1 and 5 (Table 7) were performed using 1 and 2 mol % catalyst, respectively.

Significant structural variation in the enolsilane component is also possible without loss in enantioselectivity (Table 8). Ethyl thioacetate is an alternative acetate nucleophile in this reaction, providing the aldol adduct in 97% ee when THF was employed as the solvent (entries 1, 2). To demonstrate the preparative utility of this methodology, this reaction was conducted on a 50-mmol scale employing 1 mol % of the box catalyst (Table 8, entry 2) to generate the desired adduct in quantitative yield while maintaining high enantioselectivity (97% ee). Ketone-derived enolsilanes may also be employed, as the acetone and acetophenone adducts were obtained with high enantioselectivity (entries 3−6, ≥94% ee).

The ability to conduct diastereoselective additions of substituted silylketene acetals to pyruvate esters would greatly expand the utility of this process to generate highly functionalized succinate analogues. Indeed, pyruvate esters undergo reaction

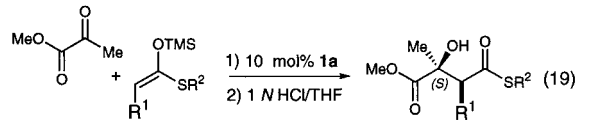
Table 8. Catalyzed Enantioselective Aldol Reactions with Methyl Pyruvate and Representative Enolsilanes (eq 18)[a]



entry	solvent	R	time	% ee[b]	% yield
1	CH_2Cl_2	EtS	12 h	86	83
2	**THF**	**EtS**	0.5 h	**97**	**97 (100)**[c]
3	CH_2Cl_2	Ph	1 d	92	80
4	**THF**	**Ph**	1 d	**99**	**77**
5	**CH_2Cl_2**	**Me**	2 d	**94**	**81**[d]
6	THF	Me	1d	93	76[d]

[a]Reactions were 0.2-0.3 M in substrate. [b]Enantiomeric excess determined by HPLC using a Chiralcel OD-H or AD column. Unless otherwise stated, the relative and absolute stereochemistry was determined by independent synthesis (see experimental). [c]Reaction performed on 50-mmol scale (1 mol% catalyst). [d]Reaction performed with benzyl pyruvate.

Table 9. Catalyzed Enantioselective Aldol Reactions between Methyl Pyruvate and Representative Enolsilanes (eq 19)[a]



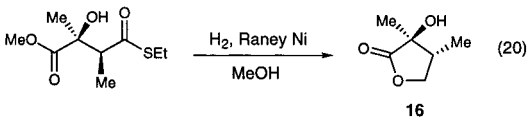
entry	solvent	R^1	R^2	enolsilane geometry[b]	time/ T (°C)	*syn:anti*[c]	ee[c] %	yield %
1	CH_2Cl_2	Me	^{t}Bu	(*Z*)	8 h/-78	94:6	96	96
2	THF	Me	^{t}Bu	(*Z*)	1 d/-78	90:10	93	93
3	CH_2Cl_2	Me	^{t}Bu	(*E*)	1 d/-78	95:5	98	90[d]
4	**THF**	**Me**	**^{t}Bu**	**(*E*)**	2 d/-78	**97:3**	**99**	**88**[d]
5	CH_2Cl_2	Me	Et	(*Z*)	4 h/-78	90:10	95	95
6	THF	Me	Et	(*Z*)	1 h/-78	94:6	93	90
7	**CH_2Cl_2**	**Me**	**Et**	**(*E*)**	2 h/-78	**98:2**	**98**	**78(93)**[e]
8	**THF**	**Me**	**Et**	**(*E*)**	2 h/-78	**98:2**	**98**	**91**
9	CH_2Cl_2	^{i}Bu	^{t}Bu	(*Z*)	2 d/-78	93:7	97[f]	58
10	**CH_2Cl_2**	**^{i}Bu**	**Et**	**(*Z*)**	1 d/-78	**90:10**[f]	**93**[f]	**88**
11	CH_2Cl_2	^{i}Pr	^{t}Bu	(*Z*)	1 d/rt	66:34[f]	97	71[g,h]
12	**CH_2Cl_2**	**^{i}Pr**	**Et**	**(*Z*)**	12 h/-50	**90:10**	**99**	**80**[h]

[a]Reactions were typically 0.2-0.3 M in substrate. [b]Isomeric purity ≥90%. [c]Product ratios determined by HPLC using a Chiralcel OD-H or AD column; enantiomeric excess is reported for the major product diastereomer. Unless otherwise stated, the relative and absolute stereochemistry was determined by independent synthesis (see experimental). [d]Reaction required 0.9 equiv of TMSOTf for complete conversion. [e]Reaction performed on a 10 mmol scale with 2.5 mol% catalyst and 0.5 equiv TMSOTf. [f]Configuration assigned by analogy. [g]Reaction required 0.5 equiv of TMSOTf for complete conversion. [h]No reaction when conducted in THF

with substituted silylketene acetals[25] in the presence of the [Cu(*t*-Bu-box)](OTf)$_2$ complex (**1a**) to provide the aldol adducts with high syn diastereoselectivity (eq 19, Table 9). Both the (*Z*) and (*E*) isomers of the illustrated propionate-derived silylketene acetals (R^1 = Me, entries 1−8) reacted in a stereoconvergent manner to provide the syn aldol adducts in excellent diastereo- and enantioselectivity (≥ 90:10 syn:anti, ≥ 93% ee). Judicious selection of solvent and silylketene acetal geometry allowed the highly diastereo- (≥ 97:3 syn:anti) and enantioselective (≥ 98% ee) production of syn substituted succinates with either the ^{t}BuS (entry 4) or EtS (entries 7, 8) thioester group. The absolute and relative stereochemistries of

(25) (a) Gennari, C.; Beretta, M. G.; Bernardi, A.; Moro, G.; Solastico, C.; Todeschini, R. *Tetrahedron* **1986**, *42*, 893−909. (b) Otera, J.; Fujita, Y.; Fukusumi, S. *Synth. Lett.* **1994**, 213-214. (c) Chan, T. H.; Aida, T.; Lau, P. W. K.; Gorys, V.; Harpp, D. N. *Tetrahedron Lett.* **1979**, 4029−4032.

these adducts were secured by conversion to the known lactone **16** (eq 20).[26]



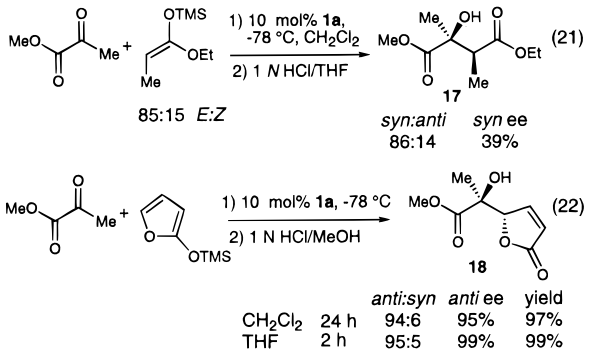
The use of silylketene acetals with larger alkyl substituents (eq 19, R^1 > Me) is also permitted. For example, the isobutyl-substituted succinate (eq 20, $R^1 = {}^i$Bu) was obtained in high selectivity (90:10 syn:anti, 93% ee) and good yield (88%, Table 9, entry 10). Even the hindered isopropyl-substituted silylketene acetal (eq 20, $R^1 = {}^i$Pr) reacted with methyl pyruvate in a highly enantioselective manner (entry 12, 90:10 syn:anti, 99% ee), although an elevated temperature (−50 °C) was necessary to achieve good conversion.

The reaction of the (*E*) silylketene acetal of *tert*-butyl thiopropionate was particularly slow in both CH_2Cl_2 and THF and would not proceed to completion without the addition of TMSOTf (Table 9, entries 3 and 4). The utilization of TMSOTf also allowed lower catalyst loadings to be employed with substituted silylketene acetals. For example, a large-scale preparation (10 mmol) was performed with (*E*)-ethyl thiopropionate silylketene acetal (Table 9, entry 7), using 2.5 mol % catalyst and 0.5 equiv TMSOTf to afford the adduct in high yield (93%) without deteriorating the selectivity (98:2 syn:anti, 98% ee).

The acetate aldol reactions were generally found to proceed with enhanced enantioselectivity and rates in THF (Tables 7 and 8). Conversely, the rates of reaction with propionate silylketene acetals were typically slower in THF, although the selectivities and yields obtained were comparable in both solvents (Table 9).[27] In general, THF is the optimal solvent with acetate-derived silylketene acetals, whereas substituted silylketene acetals perform best in CH_2Cl_2.

While thioester silylketene acetals afforded excellent results in the pyruvate aldol reaction (Table 9), the analogous ester-derived substrates proved to be inferior nucleophiles (eq 21). Reaction of methyl pyruvate with ethyl propionate trimethylsilylketene acetal catalyzed by **1a** yielded a slow and nonselective process (eq 21), the tertiary alcohol product **17** being formed with reduced diastereoselectivity (86:14 syn:anti) and low enantioselectivity (39% ee) (compare to Table 9, entry 5). On the other hand, the lactone-derived silylketene acetal, 2-(trimethylsiloxy)furan,[28] underwent facile reaction with methyl pyruvate in the presence of the catalyst **1a** to afford the anti aldol adduct **18** in high yield with excellent diastereo- and enantioselectivity (eq 22).[29] The densely functionalized product of this reaction could be a useful synthon for natural product synthesis and also may be elaborated to unnatural hexose derivatives.[28]

Although the inherent stereoconvergency of this Cu(II)-catalyzed process permits access principally to the syn aldol adducts, the corresponding anti diastereomers can be obtained using our Sn(II)-pybox-catalyzed reactions.[30] Thus, the copper



and tin catalysts together provide a powerful entry into a diverse array of substituted succinates. Furthermore, these adducts are orthogonally protected such that either the thioester or the ester can be functionalized selectively. For example, the thioester group can be readily converted to an acid, amide, or ester using either a silver-based reagent[31] or a bromination−displacement procedure.[32] Selective cleavage of a *tert*-butyl ester or a benzyl ester[33] in the presence of a thioester can also be readily accomplished. Alternatively, the Fukuyama reduction procedure (Pd/C, Et_3SiH) can be implemented to reduce thioesters to aldehydes.[34]

[Cu((*S,S*)-*i*-Pr-pybox)](SbF$_6$)$_2$ (4b). Despite the successful initial results in the methyl pyruvate aldol reaction utilizing complex **4b** (see Table 2), this catalyst did not perform well across a range of substrates (Tables 10 and 11). Decreased enantioselectivity was observed upon increasing the size of the ester (R^1, eq 23) in the pyruvate reaction component from Me (95% ee) to Et (91% ee) to Bn (84% ee), suggesting that this portion of the substrate is involved in the stereochemical course of the reaction (Table 10, entries 1−3). A sterically demanding acyl (R^2) substituent such as ^{i}Pr precludes a selective process (entry 4).

Variation of the enolsilane component was also detrimental in the Cu(II) pybox-catalyzed pyruvate aldol reactions (Table 11). Use of the silylketene acetal of ethyl thioacetate resulted in only modest enantioselection (82% ee, entry 2) relative to that with the *tert*-butyl thioester (95% ee, entry 1). Moderate diastereo- and enantioselectivity (85:15 syn:anti; 74% syn ee) were observed with a propionate-derived silylketene acetal (entry 3), clearly illustrating the limitations of the pybox catalyst in the pyruvate aldol reaction.

Catalyst Characterization and Stereochemical Models. [Cu((*S,S*)-*t*-Bu-box)](OTf)$_2$ (1a). Prior work has demonstrated that complex **1a** is an effective catalyst for the Diels−Alder reactions of α,β-unsaturated imides (eq 25).[1] Accumulated X-ray structures[10] and PM3 semiempirical calculations provide support for the dienophile−catalyst complex **19** (R = *t*-Bu), with a distorted square planar Cu(II) center. In this model, it is evident that the *re* face of the chelating dienophile is obstructed by the *tert*-butyl substituent on the ligand.

In the Cu(II)-catalyzed pyruvate aldol (eq 26), chelation of methyl pyruvate to the square planar copper center in complex **1a** affords substrate−catalyst complex **20** (R = *t*-Bu). By

(26) Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1992**, *57*, 1324−1326.

(27) With several hindered nucleophiles (eq 19, entries 11 and 12, $R^1 = {}^i$Pr), it appears that THF retards the addition step to the extent that no reaction occurs.

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

(29) Anti diastereoselectivity was also observed with this nucleophile in the Cu(II)-catalyzed (benzyloxy)acetaldehyde aldol reaction, see ref 2b. The relative stereochemistry of this adduct was confirmed by X-ray structural analysis.

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

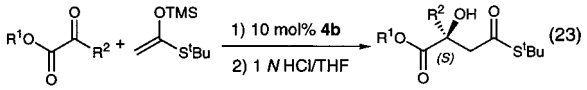
(31) Booth, P. M.; Fox, C. M. J.; Ley, S. V. *Tetrahedron Lett.* **1983**, *46*, 5143−5146.

(32) (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.

(33) Transfer hydrogenolysis can be performed in the presence of thioesters. ElAmin, B.; Anantharamaiah, M.; Royer, G. R.; Means, G. E. *J. Org. Chem.* **1979**, *44*, 3442−3444.

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

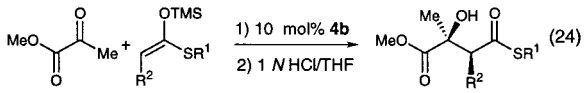
Table 10. Enantioselective Aldol Reactions with Representative Pyruvate Esters (eq 23)[a]



entry	R^1	R^2	time, (T, °C)	% ee[b]	% yield
1	Me	Me	15 min (-78)	95	92
2	Et	Me	1 h (-78)	91	91
3	Bn	Me	2 h (-78)	84	91
4	Et	^{i}Pr	16 h (-60)	2	ND

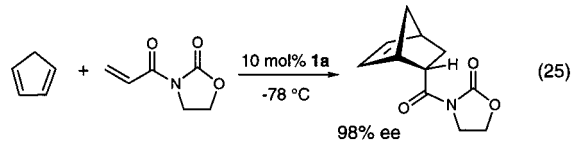
[a]All reactions were conducted in CH_2Cl_2 (0.2 M in substrate). [b]Enantiomeric excess determined by HPLC using a Chiralcel OD-H or AD column.

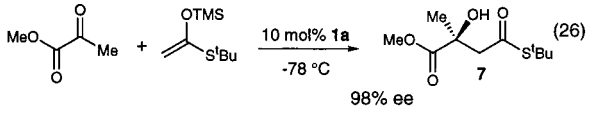
Table 11. Enantioselective Aldol Reactions of Methyl Pyruvate with Representative Enolsilanes (eq 24)[a]

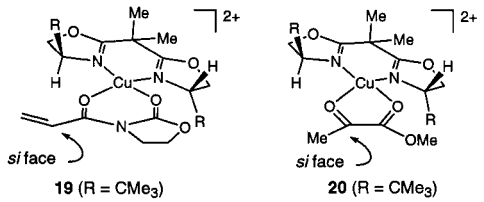


entry	R^1	R^2	time, (T, °C)	% ee[b]	% yield
1	^{t}Bu	H	15 min (-78)	95	92
2	Et	H	1 h (-78)	82	87
3	Et	Me	2 h (-50)	74[c]	ND[d]

[a]All reactions were carried out in CH_2Cl_2 (0.2 M in substrate). [b]Enantiomeric excess determined by HPLC using a Chiralcel OD-H or AD column. [c]Enantiomeric excess of the major diastereomer (*syn:anti* 85:15). [d]Reaction proceeded to full conversion.



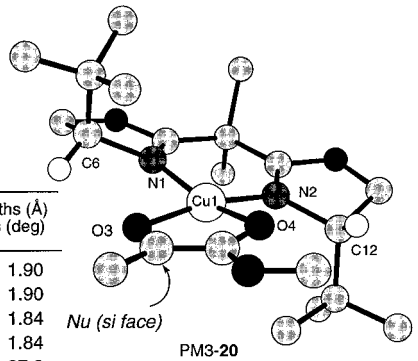




19 ($R = CMe_3$) **20** ($R = CMe_3$)

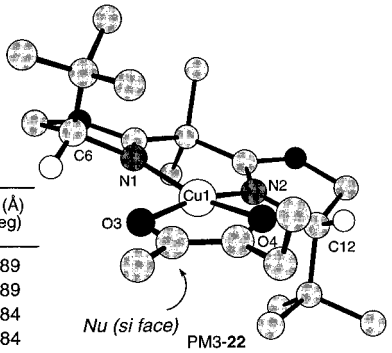
inspection, the *re* face of the coordinated ketone carbonyl is shielded by the *tert*-butyl substituent on the ligand, permitting nucleophilic attack only from the *si* face. Again, the prediction afforded by this model is in complete accord with the experimental data.

As an X-ray crystal structure of the catalyst−substrate complex was not available, PM3 semiempirical calculations were employed to generate an approximation of the [Cu((*S*,*S*)-*t*-Bu-box)(pyruvate)]$^{2+}$ complex (**20**). The accuracy of these semiempirical calculations was confirmed by reproduction of the metal geometry of the [Cu(*t*-Bu-box)$(H_2O)_2$]$(SbF_6)_2$ complex.[10] Inspection of the calculated [Cu(*t*-Bu-box)(pyruvate)]$^{2+}$ complex (PM3-**20**, Figure 1) reveals a distorted square planar copper geometry, which reaffirms the predicted model for the absolute stereochemical outcome of the pyruvate aldol reaction. It is noteworthy that the degree of distortion (~26°) found in pyruvate complex PM3-**20** is approximately that observed



Selected bond lengths (Å) and dihedral angles (deg)	
Cu1-N1	1.90
Cu1-N2	1.90
Cu1-O3	1.84
Cu1-O4	1.84
O3-Cu1-N1-C6	27.3
O4-Cu1-N2-C12	25.0

Figure 1. Computational structure of [Cu(*tert*-Bu-box)(pyruvate)]$^{2+}$ with selected bond lengths and angles.



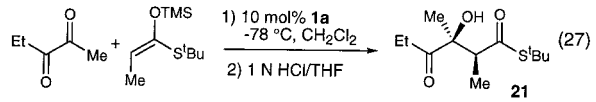
Selected bond lengths (Å) and dihedral angles (deg)	
Cu1-N1	1.89
Cu1-N2	1.89
Cu1-O3	1.84
Cu1-O4	1.84
O3-Cu1-N1-C6	26.5
O4-Cu1-N2-C12	24.9

Figure 2. Computational structure of [Cu(*t*-Bu-box)(2,3-pentanedione)]$^{2+}$ with selected bond lengths and angles.

(~33°) in the X-ray structure of the bis(aquo) complex [Cu(*t*-Bu-box)$(H_2O)_2$]$(SbF_6)_2$.[10]

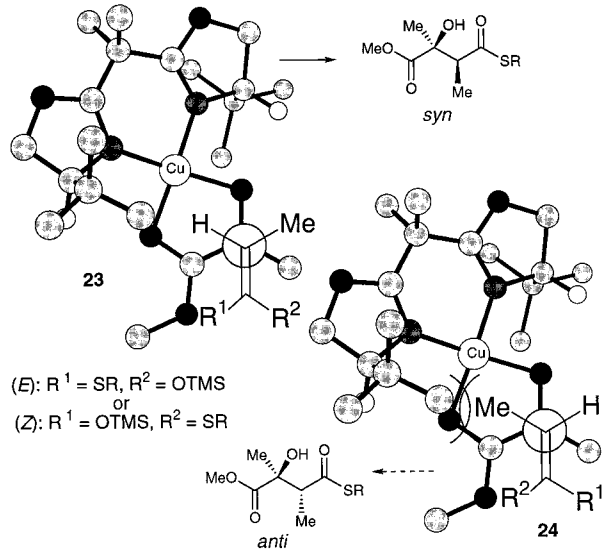
Finally, the EPR spectra of [Cu(*t*-Bu-box)]$(OTf)_2$ in the presence of methyl pyruvate clearly indicate the presence of a strong square planar copper component (see Supporting Information). Thus, these solution-phase EPR data are consistent with the solid-state structural data and calculations, which support the intermediacy of the square planar catalyst−pyruvate complex **20**.

Aldol Reactions with Diketones. The [Cu((*S*,*S*)-*t*-Bu-box)]$(OTf)_2$ complex (**1a**) can also be employed to catalyze enolsilane additions to unsymmetrical vicinal diketones (eq 27). The

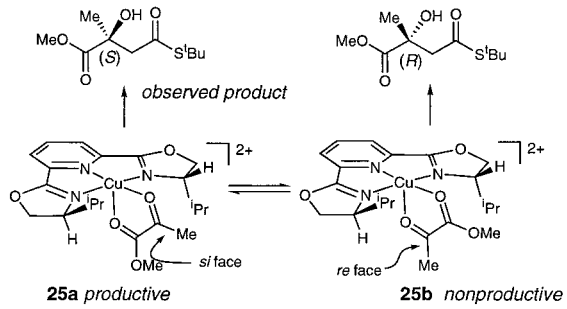


principal issue in this reaction is that of relative carbonyl reactivity differentiated by the subtle methyl vs ethyl substitution at the two reaction centers. Despite the modest bias for addition to the MeCO moiety (1.4:1) catalyzed by $TiCl_4$ (−78 °C, CH_2Cl_2), the reaction of the illustrated (*Z*) silylketene acetal to 2,3-pentanedione catalyzed by **1a** proceeded with excellent regioselectivity (98:2), diastereoselectivity (93:7), and enantioselectivity (97% ee). As may be distinguished from the computationally minimized [Cu(*t*-Bu-box)(2,3-pentanedione)]$^{2+}$ complex (**22**) (Figure 2), the ligand architecture biases those conformations of the ethyl group that block access of the nucleophile to the carbonyl moiety proximal to the ethyl group.

Scheme 4



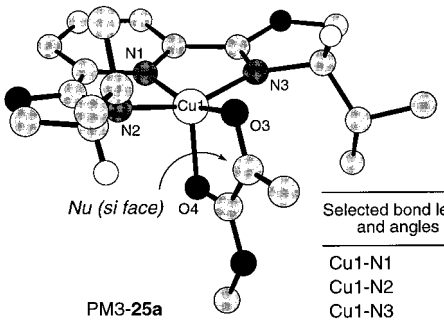
Scheme 5



Again, the calculated catalyst−substrate complex readily explains the observed carbonyl face reactivity for this family of addition reactions. The described experimental results and stereochemical model are completely consistent with the EPR spectrum of the [Cu(*t*-Bu-box)(2,3-pentanedione)](OTf)$_2$ complex, which indicated a square planar geometry (see Supporting Information).

Diastereoselectivity Models. As outlined previously, the majority of the diastereoselective pyruvate aldol reactions produced the syn adducts. This syn selectivity can be rationalized by attack of the silylketene acetal to the proposed distorted square planar Cu(II)−pyruvate complex **20** via an open transition state, which minimizes the number of repulsive gauche and dipole−dipole interactions (Scheme 4).[35] Of the three possible transition states that lead to the observed syn product, antiperiplanar transition state **23** has the fewest destabilizing interactions. By comparison, the antiperiplanar transition state that would afford the anti product **24** incurs a severe Me(nucleophile) ↔ *t*-Bu(ligand) steric interaction. An important consequence of this analysis is that both the (*E*)- and (*Z*)-silylketene acetal isomers should give rise to the same syn adduct if the R^1 and R^2 groups are of similar size; such a stereoconvergency has, indeed, been observed (see Table 9).

[Cu((*S*,*S*)-*i*-Pr-pybox)](SbF$_6$)$_2$ (4b). Based on the structural data acquired in our (benzyloxy)acetaldehyde aldol studies,[2b] we propose a model in which bidentate coordination of methyl pyruvate to the copper complex **4b** in a square pyramidal geometry accounts for the observed sense of asymmetric induction.[36] It follows that two diastereomeric catalyst−substrate complexes **25a** and **25b**, each of which predicts the opposite absolute stereochemical outcome, must be considered in the analysis of the impact of catalyst structure on reaction stereochemistry (Scheme 5). For maximal carbonyl activation, we postulate that ketone coordination occurs in the ligand plane, as illustrated in **25a**.[37] Accordingly, the catalyst−substrate complex **25a** successfully predicts the stereochemical outcome of the reactions carried out with pyruvate substrates. Although the reaction can proceed though either of the indicated complexes, the high enantioselectivity observed in the methyl pyruvate aldol reaction (95% ee) provides strong support for the assertion that the reaction proceeds principally through complex **25a**. Since an X-ray crystal structure was not available, PM3 level calculations were employed to provide a simulation of the [Cu(*i*-Pr-pybox)(pyruvate)](SbF$_6$)$_2$ complex.[38] The calculated low-energy structure depicted in Figure 3 clearly predicts nucleophilic attack from the *si* face and, as anticipated, that the equatorial position is the tighter binding site (1.84 vs. 1.92 Å). Finally, the EPR spectrum of [Cu(*i*-Pr-pybox)(pyruvate)](SbF$_6$)$_2$ indicates the presence of a square pyramidal Cu(II) center, supplying further evidence for the proposed stereochemical model **25a**.[39]



Selected bond lengths (Å) and angles (deg)

Cu1-N1	1.86
Cu1-N2	1.90
Cu1-N3	1.90
Cu1-O3	1.84
Cu1-O4	1.92
N1-Cu1-O3	160.0
N1-Cu1-O4	103.3
O3-Cu1-O4	96.7

Figure 3. Calculated structure of [Cu(*i*-Pr-pybox)(pyruvate)]$^{2+}$ with selected bond lengths and dihedral angles. The N1−Cu−O1 bond angle was constrained to 160°.

Enantioselectivity Temperature Dependence. Analysis of the temperature−enantioselectivity profiles with catalyst [Cu(*t*-Bu-box)](OTf)$_2$ (**1a**) (see Tables 5 and 12) illustrates that the observed enantioselectivities correlate well with the calculated values from Arrhenius theory (Table 12, Figure 4).[40] Eyring plots[41] of these data revealed the expected linear dependence

(35) Gennari, C. In *Comprehensive Organic Synthesis;* Trost, B. M., Fleming, I. Eds.; Pergamon Press: New York, NY, 1991; Vol. 2, Chapter 2.4.

(36) Square pyramidal structures are more common than trigonal bipyramidal structures for five-coordinate Cu(II). Cambridge Structural Database survey: 51 square pyramidal structures, 9 trigonal bipyramidal structures (http://sulfur.scs.uiuc.edu/gifs/cuii.htm). See: Hathaway, B. J. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Ed.; Pergamon Press: New York, 1987; Vol. 5, Chapter 53.

(37) As a consequence of the electronic configuration of the Cu(2$^+$) center (d^9), the square pyramidal geometry affords a strong coordinating site in the ligand plane with a weaker coordination site in the axial position. This has also been confirmed in this system by the X-ray structure of the [Cu(*i*-Pr−pybox)(DME)](SbF$_6$)$_2$ complex (ref 2b).

(38) To provide a mechanism for *simulating* the square pyramidal [Cu(pybox)(substrate)]$^{2+}$ structures, the N1−Cu−O3 bond angle was constrained during the PM3 calculations to 160°.

(39) In contrast to this square pyramidal structure, the EPR spectrum of the [Cu(*i*-Pr-pybox)]Cl$_2$ complex indicated the presence of a trigonal bipyramidal species, which was validated by the observation of the same geometry in the X-ray crystal structure of the analogous [Cu(*tert*-Bu−pybox)]Cl$_2$ complex (see Supporting Information).

Table 12. Temperature Profile of Catalyzed Pyruvate Aldol Reaction (Eq 13)

	% ee (CH_2Cl_2)		% ee (THF)	
T (°C)	expt	calcd	expt	calcd
−78	98	98	99	99
−50	95	95	97	98
−20	92	92	95	96
0	89	90	93	95
20	85	88	92	94

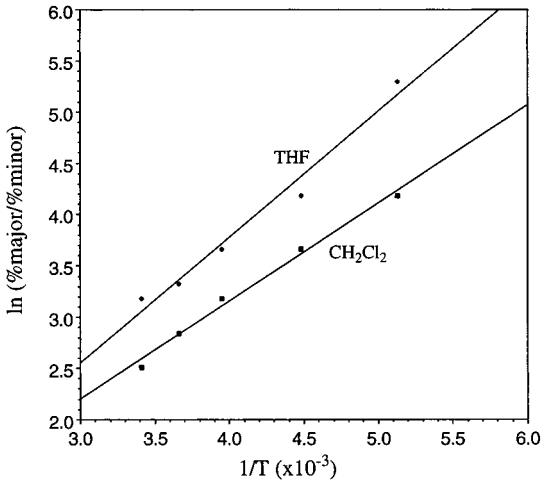
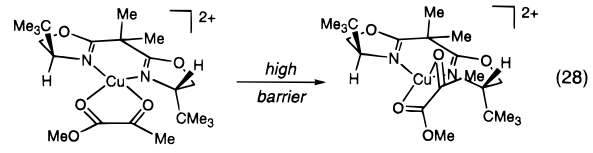


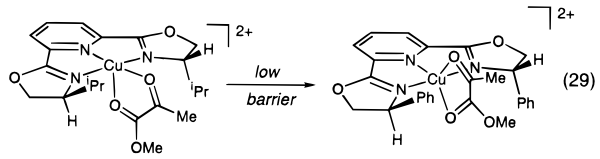
Figure 4. Eyring plot for the [Cu(*tert*-Bu-box)](OTf)$_2$-catalyzed pyruvate aldol reaction in THF and CH_2Cl_2.

of the ln(%major enantiomer/%minor enantiomer) vs reciprocal temperature ($R^2_{THF} = 0.976$; $R^2_{CH_2Cl_2} = 0.993$).

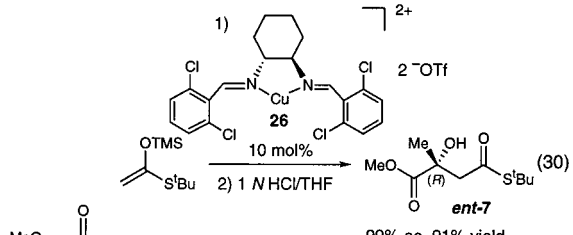
These data support the assertion that only two diastereomeric transition states account for the observed selectivities and, by corollary, provide evidence against the presence of competitive alternate geometries. By comparison, the pyruvate aldol reaction catalyzed by the [Cu(*i*-Pr-pybox)](SbF$_6$)$_2$ catalyst (**4b)** exhibits a poor temperature−enantioselectivity profile (−78 °C, 95% ee; −50 °C, 86% ee; −17 °C, 49% ee; +20 °C, 26% ee), which signals the intervention of other catalyst−substrate species.[42] To date, the only Cu(II)-catalyzed reactions which follow an Arrhenius analysis proceed via square planar catalyst−substrate complexes, i.e., the pyruvate aldol and the Diels−Alder reactions[1] catalyzed by [Cu(*t*-Bu-box)](X)$_2$ complexes. Apparently, the high barrier for distortion from the square planar → tetrahedral geometry (eq 28) confers the requisite torsional rigidity needed to enforce uniform binding modes, even at elevated temperatures. The inferior temperature profile results observed in the pybox−Cu(II)-catalyzed reactions are consistent with the more facile deformability of five-coordinate Cu(II) complexes (i.e., the reported low barrier for distortion from square pyramidal → trigonal bipyramidal, eq 29), as compared to their four-coordinate counterparts.[43]

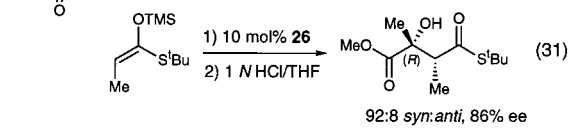
Bis(imine)-Derived Catalysts in the Aldol Reactions of Pyruvate Esters. We have previously documented the utility





of *trans*-1,2-cyclohexanebis(imine)-derived copper catalysts in the Diels−Alder cycloaddition reaction.[44] The catalyst derived from the *trans*-1,2,-cyclohexanebis(2,6-dichlorobenzylimine) and Cu(OTf)$_2$ (**26**) mediated the pyruvate aldol reaction (eq 30) in >99% ee and 91% yield (1 h, −78 °C, CH_2Cl_2). In addition, the (*R*) configuration of the product ***ent*-7** complements the (*S*) stereochemistry obtained using the [Cu(*t*-Bu-box)](OTf)$_2$ (**1a**) catalyst. The stereochemical outcome observed with the bis(imine)-derived catalysts may be rationalized by invoking a square planar catalyst−substrate complex, in analogy to that proposed in our Diels−Alder studies.[1]





Unfortunately, the scope of the pyruvate aldol reactions with the bis(imine) copper catalyst **26** was not as general as that with the box-derived catalyst. The reaction of a propionate-derived silylketene acetal (eq 31) proceeded with 92:8 syn:anti diastereoselectivity and 86% ee compared to 94:6 syn:anti diastereoselectivity and 96% ee with [Cu(*t*-Bu-box)](OTf)$_2$ (10 mol %, CH_2Cl_2, −78 °C). Despite the lack of generality, the bisimine catalyst **26** may be a useful alternative in certain instances where product enrichment could easily be achieved through either product crystallization or diastereomer resolution.

Conclusions

This study documents the first example of catalytic enantioselective additions of enolsilanes to pyruvate esters. The C_2-symmetric copper(II) complex [Cu((*S*,*S*)-*t*-Bu-box)](OTf)$_2$ (**1a**) has been found to be an excellent catalyst for this transformation, providing functionalized hydroxysuccinate derivatives in high

(40) Theoretical enantioselectivities were calculated from the results obtained experimentally at −78 °C assuming that the enantioselection was only a reflection of the energy differences between two diastereomeric transition states.

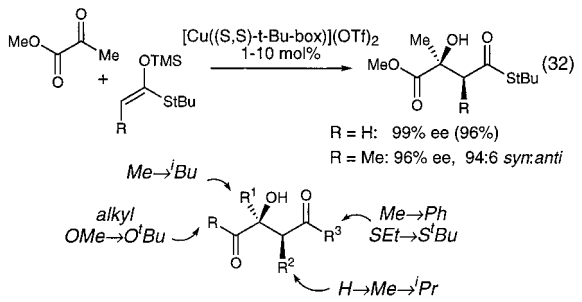
(41) Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 477−515.

(42) We have observed a similar temperature profile in the [Cu(Ph-pybox)](SbF$_6$)$_2$ catalyzed aldol reaction of (benzyloxy)acetaldehyde, see ref 2b.

(43) (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.

(44) (a) Evans, D. A.; Lectka, T.; Miller, S. J. *Tetrahedron Lett.* **1993**, *34*, 7027−7030. The Cu(I) complexes of these ligands have also been employed as atom-transfer catalysts in aziridination and cyclopropanation reactions: (b) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326−5327. (c) Li, Z.; Quan, R. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5889−5890.

diastereo- and enantioselectivity using as little as 1 mol % catalyst (eq 32).



This methodology has been demonstrated to be preparatively useful by the execution of a pyruvate aldol reaction on a 50-mmol scale. Additionally, both the nucleophilic and electrophilic components can be broadly altered, permitting access to a large library of enantiopure succinates. The scope of this reaction was extended to include regioselective additions of silylketene acetals to 1,2-diketones.

Mechanistic insight into the pyruvate aldol reaction has also been gained. Silyl crossover experiments demonstrated that the silyl-transfer step is intermolecular. Based upon these results, TMSOTf has been identified as an addend to accelerate these reactions. Furthermore, solvent was shown to have a dramatic impact on the rates of addition and catalyst turnover in the pyruvate aldol reaction. Crystallographic structures and semi-empirical calculations provided insight into the mode of stereochemical induction, allowing the construction of a model in which chelation of the pyruvate ester to the copper complex in a square planar geometry (**20**) accounts for the observed sense of asymmetric induction. Two other Cu(II) complexes, **4b** and **26,** have been evaluated as enantioselective catalysts for the pyruvate aldol reaction; however, the scope of the process with these systems lacked generality.

Experimental Section[45]

General Procedure for the Preparation of Ketene Acetals. General procedures for the preparation of the desired silylketene acetals are included in the preceding paper.[2b]

General Procedure for the Addition of Silylketene Acetals to Pyruvates Catalyzed by [Cu((*S*,*S*)-*t*-Bu-box)](OTf)$_2$ (1a). To an oven-dried 10-mL round-bottom flask containing a magnetic stirring bar were added, in an inert atmosphere box, (*S*,*S*)-bis(*tert*-butyloxazoline)[10] (15 mg, 0.050 mmol) and Cu(OTf)$_2$ (18 mg, 0.050 mmol). The flask was fitted with a serum cap, removed from the inert atmosphere box, and charged with solvent (1.5−3.0 mL). The resulting suspension was stirred rapidly for 4 h with CH_2Cl_2 to give a slightly cloudy bright green solution or 1 h with THF to give a clear dark green solution. The catalyst was cooled to −78 °C, and the pyruvate (0.50 mmol) was added, followed by the silylketene acetal (0.60 mmol). The resulting solution was stirred at −78 °C until the pyruvate was completely consumed (0.5−24 h), as determined by TLC (2.5% diethyl ether/CH_2Cl_2). The reaction mixture was then filtered through a 2- × 4-cm plug of silica gel with Et_2O (60 mL). Concentration of the ether solution gave the crude silyl ether which was dissolved in THF (5 mL) and treated with 1 N HCl (1 mL). After being stirred at room temperature for 1−5 h, this solution was poured into a separatory funnel and diluted with Et_2O (20 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 Na_2SO_4, filtered, and concentrated to provide the crude hydroxy esters. Purification by flash chromatography provided the title compounds.

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

Preparation of (*S*)-*tert*-Butyl 3-Hydroxy-3-methoxycarbonylbutanethioate (7, Table 7, Entry 1). Compound **7** was prepared according to the general procedure (1.5 mL of THF; 2 h at −78 °C) using the silylketene acetal derived from *tert*-butyl thioacetate (153 μL, 0.60 mmol) and methyl pyruvate (45 μL, 0.50 mmol) to provide the pure product **7** as a clear oil in 96% yield (112 mg, 0.48 mmol) after flash chromatography with 10−20% EtOAc/hexanes. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (99:1 hexanes/2-propanol); 0.5 mL/min): (*S*) enantiomer t_r = 13.4 min; (*R*) enantiomer t_r = 12.7 min; 99% ee; $[\alpha]^{rt}_D$ +25.1 (*c* 5.2, $CHCl_3$); IR (CH_2Cl_2) 3534, 2967, 1738, 1678 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 3.70 (br s, 1H), 3.02 (d, J = 15.8 Hz, 1H), 2.79 (d, J = 15.8 Hz, 1H), 1.40 (s, 9H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 175.7, 72.9, 52.9, 52.7, 48.6, 29.6, 26.0; LRMS (CI/NH_3) *m*/*z* 235 $(MH)^+$, 252 $(M + NH_4)^+$; HRMS (CI/NH_3) exact mass calcd for $(C_{10}H_{18}O_4S + NH_4)^+$ requires *m*/*z* 252.1270, found *m*/*z* 252.1268.

Preparation of (*S*)-*tert*-Butyl 3-Hydroxy-3-methoxycarbonylbutanethioate Using Catalyst 4b (7, Table 9, Entry 1). To an oven-dried 10-mL round-bottom flask containing a magnetic stirring bar were added, in an inert atmosphere box, (*S*,*S*)-bis(isopropyloxazolinyl)-pyridine (15.1 mg, 0.050 mmol) and $CuCl_2$ (6.7 mg, 0.050 mmol). To a second oven-dried 10-mL round-bottom flask containing a magnetic stirring bar was added, in an inert atmosphere box, $AgSbF_6$ (34.0 mg, 0.10 mmol). The flasks were fitted with serum caps and removed from the inert 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 clear green solution which was added via cannula followed by a 0.5-mL CH_2Cl_2 rinse to the $AgSbF_6$ (in 0.5 mL CH_2Cl_2) with vigorous stirring. The resulting mixture was covered with aluminum foil, stirred rapidly for 3 h, 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 precipitated (white) AgCl. The electric blue catalyst solution was cooled to −78 °C, and methyl pyruvate (45 μL, 0.50 mmol) was added, followed by silylketene acetal **3** (153 μL, 0.60 mmol). The resulting solution was stirred at −78 °C for 15 min, at which time TLC analysis (2.5% diethyl ether/CH_2Cl_2) indicated that the methyl pyruvate was completely consumed. The reaction mixture was then worked-up as described above for the reaction employing **1a**. Purification by flash chromatography provided the title compound **7** as a pale yellow oil in 92% yield (108 mg, 0.46 mmol) after flash chromatography with 10−20% EtOAc/hexanes: $[\alpha]^{rt}_D$ +23.2° (*c* 5.2, $CHCl_3$). Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (99:1 hexanes/2-propanol; 0.5 mL/min): (*S*) enantiomer t_r = 13.4 min; (*R*) enantiomer t_r = 12.7 min; 95% ee.

The analytical data obtained from this material (^{1}H NMR, ^{13}C NMR, and HRMS) were identical to those described above: $[\alpha]^{rt}_D$ +23.2° (*c* 5.2, $CHCl_3$).

Other pyruvate aldol reactions with the [Cu(*i*-Pr-pybox)]$(SbF_6)_2$ catalyst (**4b**) were performed analogously using the indicated silylketene acetal and pyruvate ester.

Preparation of (*R*)-*tert*-Butyl 3-Hydroxy-3-methoxycarbonylbutanethioate Using Catalyst 26 (7, Eq 30). A similar procedure was used to prepare the 1,2-cyclohexanediamine(bisimine) catalyst (**26**) as has been previously described.[44] To an oven-dried round-bottom flask containing a magnetic stirring bar were added, in a nitrogen atmosphere box, the bisimine ligand (21.4 mg, 0.05 mmol) and Cu(OTf)$_2$ (18.1 mg, 0.05 mmol). The flask was fitted with a serum cap, removed from the nitrogen atmosphere box, and charged with CH_2Cl_2 (3.0 mL). The resulting suspension was stirred rapidly for 4 h to yield a clear dark blue solution which was then cooled to −78 °C. Methyl pyruvate (45 μL, 0.50 mmol) was added, followed by the silylketene acetal of *tert*-butyl thioacetate (153 μL, 0.60 mmol). The reaction mixture was stirred at −78 °C for 3 h, at which time TLC analysis (2.5% Et_2O/CH_2Cl_2) indicated that the methyl pyruvate had been completely consumed. The reaction mixture was then worked-up as described above for the reaction employing **1a**. Purification by flash chromatography with 10−20% EtOAc/hexanes provided the title compound **7** as a pale yellow oil in 91% yield (106 mg, 0.45 mmol). Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (99:1 hexanes/2-propanol;

0.5 mL/min): (*S*) enantiomer $t_r = 13.4$ min; (*R*) enantiomer $t_r = 12.7$ min; 99.6% ee.

The analytical data obtained from this material (^{1}H 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: $[\alpha]^{rt}_D$ −23.5 (*c* 4.7, $CHCl_3$).

Preparation of (*S*)-*tert*-Butyl 3-Benzyloxycarbonyl-3-hydroxybutanethioate (Table 7, Entry 2). This compound was prepared according to the general procedure (1.5 mL of THF) using the silylketene acetal derived from *tert*-butyl thioacetate (153 μL, 0.60 mmol) and benzyl pyruvate (81 μL, 0.50 mmol) to provide the pure product as a clear oil in 95% yield (147 mg, 0.47 mmol) after flash chromatography with 10−15% EtOAc/hexanes. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (99:1 hexanes/2-propanol; 1.0 mL/min): (*S*) enantiomer $t_r = 11.0$ min; (*R*) enantiomer $t_r = 9.9$ min; 99% ee; $[\alpha]^{rt}_D$ −18.1 (*c* 3.0, $CHCl_3$); IR (neat) 3518, 2963, 2925, 1740, 1681 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.32 (m, 5H), 5.21 (s, 2H), 3.75 (br s, 1H), 3.10 (d, $J = 16.1$ Hz, 1H), 2.85 (d, $J = 16.1$ Hz, 1H), 1.42 (s, 9H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 175.3, 135.3, 128.5, 128.3, 128.2, 72.9, 67.5, 52.9, 48.7, 29.7, 26.1; LRMS (FAB) *m*/*z* 311 $(MH)^+$, 333 $(M + Na)^+$; HRMS (FAB) exact mass calcd for $(C_{16}H_{22}O_4S + Na)^+$ requires *m*/*z* 333.1137, found *m*/*z* 333.1128.

Preparation of (*S*)-*tert*-Butyl 3-*tert*-Butyloxycarbonyl-3-hydroxybutanethioate (Table 7, Entry 3). This compound was prepared according to the general procedure (1.5 mL of THF) using the silylketene acetal derived from *tert*-butyl thioacetate (153 μL, 0.60 mmol) and *tert*-butyl pyruvate (59 μL, 0.50 mmol) to provide the pure product as a clear oil in 91% yield (125 mg, 0.45 mmol) after flash chromatography with 10−20% EtOAc/hexanes. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (99:1 hexanes/EtOAc; 0.5 mL/min): (*S*) enantiomer $t_r = 16.1$ min; (*R*) enantiomer $t_r = 15.1$ min; 99% ee; $[\alpha]^{rt}_D$ +0.52 (*c* 2.6, $CHCl_3$); IR (neat) 3511, 2978, 2926, 1731, 1684 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (br s, 1H), 3.01 (d, $J = 16.1$ Hz, 1H), 2.78 (d, $J = 16.1$ Hz, 1H), 1.47 (s, 9H), 1.44 (s, 9H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 174.5, 82.3, 72.8, 53.0, 48.5, 29.7, 27.8, 26.2; LRMS (CI/NH_3) *m*/*z* 277 $(MH)^+$, 294 $(M + NH_4)^+$; HRMS (CI/NH_3) exact mass calcd for $(C_{13}H_{24}O_4S + NH_4)^+$ requires *m*/*z* 294.1739, found *m*/*z* 294.1731.

Preparation of (*S*)-*tert*-Butyl 3-Hydroxy-3-methoxycarbonylpentanethioate (Table 7, Entry 4). This compound was prepared according to the general procedure (1.5 mL of THF) using the silylketene acetal derived from *tert*-butyl thioacetate (153 μL, 0.60 mmol) and methyl 2-ketobutyrate (54 μL, 0.50 mmol) to provide the pure product as a clear oil in 84% yield (104 mg, 0.42 mmol) after flash chromatography with 10−15% EtOAc/hexanes. Enantiomeric excess was determined by GC with a CYCLODEX-B column (115 °C, 25 psi): (*S*) enantiomer $t_r = 44.1$ min; (*R*) enantiomer $t_r = 43.3$ min; 94% ee; $[\alpha]^{rt}_D$ +14.8 (*c* 2.3, $CHCl_3$); IR (neat) 3519, 2966, 2923, 1738, 1685 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 3.61 (br s, 1H), 3.00 (d, $J = 15.7$ Hz, 1H), 2.83 (d, $J = 15.7$ Hz, 1H), 1.66 (m, 2H), 1.42 (s, 9H), 0.85 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 175.5, 75.9, 52.7, 52.1, 48.6, 32.1, 29.7, 7.4; LRMS (CI/NH_3) *m*/*z* 249 $(MH)^+$, 266 $(M + NH_4)^+$; HRMS (CI/NH_3) exact mass calcd for $(C_{11}H_{20}O_4S + NH_4)^+$ requires *m*/*z* 266.1426, found *m*/*z* 266.1419.

Preparation of (*S*)-*tert*-Butyl 3-Hydroxy-3-methoxycarbonyl-5-methylhexanethioate (Table 7, Entry 5). This compound was prepared according to the general procedure (1.5 mL of THF) using the silylketene acetal derived from *tert*-butyl thioacetate (153 μL, 0.60 mmol) and methyl 2-keto-4-methylpentanoate (72 mg, 0.50 mmol) to provide the pure product as a clear oil in 94% yield (130 mg, 0.47 mmol) after flash chromatography with 10−15% EtOAc/hexanes. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (99:1 hexanes/EtOAc; 1.0 mL/min): (*S*) enantiomer $t_r = 12.3$ min; (*R*) enantiomer $t_r = 11.5$ min; 94% ee; $[\alpha]^{rt}_D$ +7.6 (*c* 6.3, $CHCl_3$); IR (neat) 3522, 2958, 2870, 1740, 1683 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 3.63 (br s, 1H), 2.97 (d, $J = 15.6$ Hz, 1H), 2.81 (d, $J = 15.6$ Hz, 1H), 1.74 (m, 1H), 1.58 (dd, $J = 1.7$, 6.1 Hz, 2H), 1.42 (s, 9H), 0.92 (d, $J = 6.6$ Hz, 3H), 0.82 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 175.8, 75.6, 53.4, 52.6, 48.6, 47.5, 29.7, 24.2, 23.8, 23.3; LRMS (CI/NH_3) *m*/*z* 277 $(MH)^+$, 294 $(M + NH_4)^+$; HRMS (CI/NH_3) exact mass calcd for $(C_{13}H_{24}O_4S + NH_4)^+$ requires *m*/*z* 294.1739, found *m*/*z* 294.1730.

Preparation of (*R*)-*tert*-Butyl 3-Ethoxycarbonyl-3-hydroxy-4-methylpentanethioate (Table 7, Entry 6). This compound was prepared according to the general procedure (1.5 mL of THF) using the silylketene acetal derived from *tert*-butyl thioacetate (153 μL, 0.60 mmol) and ethyl 3-methyl-2-oxobutyrate (73 μL, 0.50 mmol) to provide the pure product as a clear oil in 84% yield (116 mg, 0.42 mmol) after flash chromatography with 10% EtOAc/hexanes. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (99:1 hexanes/EtOAc; 1.0 mL/min): (*S*) enantiomer $t_r = 11.0$ min; (*R*) enantiomer $t_r = 9.6$ min; 36% ee; $[\alpha]^{rt}_D$ −1.0 (*c* 4.8, $CHCl_3$); IR (CH_2Cl_2) 3520, 2968, 1730, 1681 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (m, 2H), 3.52 (br s, 1H), 2.94 (d, $J = 15.8$ Hz, 1H), 2.89 (d, $J = 15.8$ Hz, 1H), 1.85 (septet, $J = 6.8$ Hz, 1H), 1.40 (s, 9H), 1.27 (t, $J = 7.1$ Hz, 3H), 0.91 (d, $J = 6.8$ Hz, 3H), 0.87 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 175.1, 76.7, 61.7, 50.4, 48.4, 35.4, 29.6, 16.9, 16.1, 14.1; LRMS (CI/NH_3) *m*/*z* 277 $(MH)^+$, 294 $(M + NH_4)^+$; HRMS (CI/NH_3) exact mass calcd for $(C_{13}H_{24}O_4S + NH_4)^+$ requires *m*/*z* 294.1739, found *m*/*z* 2294.1728.

Preparation of (*S*)-Ethyl 3-Hydroxy-3-methoxycarbonylbutanethioate (Table 8, Entry 2). This compound was prepared according to the general procedure (1.5 mL of THF; 0.5 h at −78 °C) using the silylketene acetal derived from ethyl thioacetate (133 μL, 0.60 mmol) and methyl pyruvate (45 μL, 0.50 mmol) to provide the pure product as a colorless oil in 97% yield (100 mg, 0.48 mmol) after flash chromatography with 10−20% EtOAc/hexanes. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (99:1 hexanes/2-propanol; 1.0 mL/min): (*S*) enantiomer $t_r = 17.6$ min; (*R*) enantiomer $t_r = 15.6$ min; 97% ee; $[\alpha]^{rt}_D$ +25.3 (*c* 4.8, $CHCl_3$); IR (neat) 3508, 2944, 1738, 1685 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 3.67 (br s, 1H), 3.13 (d, $J = 15.9$ Hz, 1H), 2.91 (d, $J = 15.9$ Hz, 1H), 2.85 (q, $J = 7.4$ Hz, 2H), 1.40 (s, 3H), 1.21 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 175.8, 72.9, 52.9, 52.7, 26.2, 23.4, 14.5; LRMS (CI/NH_3) *m*/*z* 207 $(MH)^+$, 224 $(M + NH_4)^+$; HRMS (CI/NH_3) exact mass calcd for $(C_8H_{14}O_4S + NH_4)^+$ requires *m*/*z* 224.0957, found *m*/*z* 224.0963.

Large-Scale Preparation of (*S*)-Ethyl 3-Hydroxy-3-methoxycarbonylbutanethioate (Table 8, Entry 2). To an oven-dried 100-mL round-bottom flask containing a magnetic stirring bar were added, in a nitrogen atmosphere box, (*S*,*S*)-bis(*tert*-butyloxazoline) (147 mg, 0.50 mmol) and $Cu(OTf)_2$ (181 mg, 0.50 mmol). The flask was fitted with a serum cap, removed from the nitrogen atmosphere box, and charged with THF (15 mL). The resulting suspension was stirred rapidly for 1 h to give a clear dark green solution. The catalyst solution (1 mol %) was cooled to −90 °C (liquid N_2/hexane bath), and methyl pyruvate (4.5 mL, 50 mmol) was added. A temperature probe was inserted, and the silylketene acetal derived from ethyl thioacetate (13.2 mL, 60 mmol) was added such that the temperature remained ≤−80 °C (∼20 min addition). After the solution was stirred an additional 3 h at −78 °C (dry ice/acetone bath), TLC analysis (2.5% Et_2O/CH_2Cl_2) indicated that the methyl pyruvate had been completely consumed. The reaction mixture was then filtered through a 5- × 10-cm plug of silica gel with Et_2O (600 mL). Concentration of the ether solution gave the crude silyl ether, which was dissolved in THF (100 mL) and treated with 1 N HCl (20 mL). After being stirred at room temperature for 1 h, this solution was poured into a separatory funnel and diluted with Et_2O (600 mL). After mixing, the aqueous layer was discarded, and the ether layer was washed with saturated aqueous $NaHCO_3$ (150 mL) and brine (150 mL). The resulting ether layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to provide the crude hydroxy ester. Flash chromatography with 10−20% EtOAc/hexanes provided the pure product as a colorless oil in 100% yield (10.3 g, 50 mmol). Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (99:1 hexanes/2-propanol; 1.0 mL/min; (*S*) enantiomer $t_r = 17.6$ min; (*R*) enantiomer $t_r = 15.6$ min; 97% ee.

Preparation of (*S*)-Methyl 2-Hydroxy-2-methyl-4-oxo-4-phenylbutanoate (Table 8, Entry 4). This compound was prepared according to the general procedure (1.5 mL of THF; 1 day at −78 °C) using the enolsilane derived from acetophenone (123 μL, 0.60 mmol) and methyl pyruvate (45 μL, 0.50 mmol) to provide the pure product

as a yellow oil in 77% yield (85 mg, 0.38 mmol) after flash chromatography with 25−30% EtOAc/hexanes. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (96:4 hexanes/2-propanol; 1.0 mL/min): (*S*) enantiomer $t_r = 24.4$ min; (*R*) enantiomer $t_r = 20.6$ min; 99% ee; $[\alpha]^{rt}_D$ +84.4 (*c* 3.5, $CHCl_3$); IR (neat) 3507, 2984, 2955, 1742, 1684 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94−7.43 (m, 5H), 3.99 (br s, 1H), 3.75 (s, 3H), 3.65 (d, $J = 17.7$ Hz, 1H), 3.34 (d, $J = 17.7$ Hz, 1H), 1.50 (s, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 176.3, 136.2, 133.7, 128.6, 128.1, 72.6, 52.7, 47.9, 26.4; LRMS (CI/NH_3) *m*/*z* 223 $(MH)^+$, 240 $(M + NH_4)^+$; HRMS (CI/NH_3) exact mass calcd for $(C_{12}H_{14}O_4 + NH_4)^+$ requires *m*/*z* 240.1236, found *m*/*z* 240.1235.

Preparation of (*S*)-Benzyl 2-Hydroxy-2-methyl-4-oxopentanoate (Table 8, Entry 5). This compound was prepared according to the general procedure (1.5 mL of CH_2Cl_2, 2 days at −78 °C) using the enolsilane derived from acetone (200 μL, 1.0 mmol, 85% pure) and benzyl pyruvate (81 μL, 0.50 mmol) to provide the pure product as a clear oil in 81% yield (95 mg, 0.40 mmol) after flash chromatography with 30−50% EtOAc/hexanes. Enantiomeric excess was determined by GC with a GTA column (140 °C, 20 psi): (*S*) enantiomer $t_r = 15.9$ min; (*R*) enantiomer $t_r = 15.1$ min; 94% ee; $[\alpha]^{rt}_D$ +42.9 (*c* 3.7, $CHCl_3$); IR (neat) 3506, 2982, 1734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5H), 5.19 (s, 2H), 3.85 (br s, 1H), 3.12 (d, $J = 17.8$ Hz, 1H), 2.79 (d, $J = 17.8$ Hz, 1H), 2.12 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.6, 175.5, 135.3, 128.5, 128.3, 128.1, 72.5, 67.3, 52.2, 30.4, 26.0; LRMS (CI/NH_3) *m*/*z* 237 $(MH)^+$, 254 $(M + NH_4)^+$; HRMS (CI/NH_3) exact mass calcd for $(C_{13}H_{16}O_4 + NH_4)^+$ requires *m*/*z* 254.1392, found *m*/*z* 254.1388.

(2*S*,3*S*)-*tert*-Butyl 3-Hydroxy-3-methoxycarbonyl-2-methylbutanethioate (Table 9, Entries 1 and 4). (A) From the (*Z*)-Silylketene Acetal Isomer. This compound was prepared according to the general procedure (3.0 mL of CH_2Cl_2; 8 h at −78 °C) employing the silylketene acetal derived from *tert*-butyl thiopropionate as a 95:5 mixture of *Z*:*E* isomers (149 μL, 0.60 mmol) and methyl pyruvate (45 μL, 0.50 mmol) to provide the pure product as a colorless oil in 96% yield (119 mg, 0.48 mmol) after flash chromatography with 10−20% EtOAc/hexanes: 94:6 syn:anti, 96% syn ee; $[\alpha]^{rt}_D$ +58.8° (*c* 3.9, $CHCl_3$).

(B) From the (*E*)-Silylketene Acetal Isomer. This compound was prepared according to the general procedure (1.5 mL of THF; 2 days at −78 °C) employing the silylketene acetal derived from *tert*-butyl thiopropionate as a 96:4 mixture of *E*:*Z* isomers (149 μL, 0.60 mmol) and methyl pyruvate (45 μL, 0.50 mmol). After 24 h at −78 °C, TLC analysis indicated that the reaction was not complete, so TMSOTf (87 μL, 0.45 mmol) was added slowly to the reaction. The consumption of methyl pyruvate was complete within 48 h. The reaction mixture was quenched with solid $NaHCO_3$ (∼100 mg) at −78 °C and then treated as described in the general procedure. The title compound was obtained as a colorless oil in 88% yield (111 mg, 0.44 mmol) after flash chromatography with 10−20% EtOAc/hexanes: 97:3 syn:anti, 99% syn ee; $[\alpha]^{rt}_D$ +62.2 (*c* 4.8, $CHCl_3$).

Product ratios were determined by HPLC with a Chiralcel OD-H column (99:1 hexanes/2-propanol; 1.0 mL/min): anti enantiomers $t_r = 5.2$, 5.4 min; *syn*-(2*R*,3*R*) $t_r = 6.6$ min; *syn*-(2*S*,3*S*) $t_r = 7.3$ min. Syn isomer: IR (neat) 3508, 2964, 2892, 1733, 1682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 3.62 (br s, 1H), 2.90 (q, $J = 7.2$ Hz, 1H), 1.423 (s, 3H), 1.420 (s, 9H), 1.17 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8, 175.0, 75.8, 55.4, 52.7, 48.5, 29.5, 24.6, 13.6; LRMS (CI/NH_3) *m*/*z* 249 $(MH)^+$, 266 $(M + NH_4)^+$; HRMS (CI/NH_3) exact mass calcd for $(C_{11}H_{20}O_4S + H)^+$ requires *m*/*z* 249.1161, found *m*/*z* 249.1164.

Preparation of (2*S*,3*S*)-Ethyl 3-Hydroxy-3-methoxycarbonyl-2-methylbutanethioate (Table 9, Entries 6 and 8). (A) From the (*Z*)-Silylketene Acetal Isomer. This compound was prepared according to the general procedure (1.5 mL ofTHF; 1 h at −78 °C) employing the silylketene acetal derived from ethyl thiopropionate as a 95:5 mixture of *Z*:*E* isomers (130 μL, 0.60 mmol) and methyl pyruvate (45 μL, 0.50 mmol) to provide the pure product as a colorless oil in 90% yield (99 mg, 0.45 mmol) after flash chromatography with 15−25% EtOAc/hexanes; 94:6 syn:anti, 93% syn ee; $[\alpha]^{rt}_D$ +45.0° (*c* 4.8, $CHCl_3$).

(B) From the (*E*)-Silylketene Acetal Isomer. This compound was prepared according to the general procedure (1.5 mL of THF; 2 h at −78 °C) employing the silylketene acetal derived from ethyl thiopropionate as a >95:5 mixture of *E*:*Z* isomers (130 μL, 0.60 mmol) and methyl pyruvate (45 μL, 0.50 mmol) to provide the pure product as a colorless oil in 91% yield (100 mg, 0.45 mmol) after flash chromatography with 15−25% EtOAc/hexanes: 98:2 syn:anti, 98% syn ee; $[\alpha]^{rt}_D$ +43.2 (*c* 15.5, $CHCl_3$).

Product ratios were determined by HPLC with a Chiralcel OD-H column (95:5 hexanes/EtOAc; 1.0 mL/min): anti enantiomers $t_r = 8.5$, 9.4 min; *syn*-(2*R*,3*R*) $t_r = 11.8$ min; *syn*-(2*S*,3*S*) $t_r = 12.8$ min. Syn isomer: IR (neat) 3508, 2964, 2882, 1733, 1682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 3H), 3.57 (br s, 1H), 2.93 (q, $J = 7.2$ Hz, 1H), 2.78 (q, $J = 7.4$ Hz, 2H), 1.35 (s, 3H), 1.14 (d, $J = 7.2$ Hz, 3H), 1.14 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.5, 174.9, 75.5, 55.4, 52.6, 24.2, 23.2, 14.3, 13.4; LRMS (CI/NH_3) *m*/*z* 221 $(MH)^+$, 238 $(M + NH_4)^+$; HRMS (CI/NH_3) exact mass calcd for $(C_9H_{16}O_4S + NH_4)^+$ requires *m*/*z* 238.1113, found *m*/*z* 238.1116.

Large-Scale Preparation of (2*S*,3*S*)-Ethyl 3-Hydroxy-3-methoxycarbonyl-2-methylbutanethioate (Table 9, Entry 7). To an oven-dried 50-mL round-bottom flask containing a magnetic stirring bar were added, in a nitrogen atmosphere box, (*S*,*S*)-bis(*tert*-butyloxazoline) (71 mg, 0.24 mmol) and $Cu(OTf)_2$ (87 mg, 0.24 mmol). The flask was fitted with a serum cap, removed from the nitrogen atmosphere box, and charged with CH_2Cl_2 (10 mL). The resulting suspension was stirred rapidly for 4 h to give a slightly cloudy green solution. The catalyst solution (2.5 mol %) was cooled to −78 °C, and methyl pyruvate (0.86 mL, 9.5 mmol) was added, followed by the silyl ketene acetal derived from ethyl thiopropionate as a >95:5 mixture of *E*:*Z* isomers (2.20 mL, 10.0 mmol). After 15 h at −78 °C, TLC analysis indicated that the reaction was not complete, so TMSOTf (0.90 mL, 4.90 mmol) was added slowly to the reaction. The consumption of methyl pyruvate was complete within 2 h. The solution was diluted with CH_2Cl_2 (15 mL) and quenched with saturated aqueous $NaHCO_3$ (15 mL) at 0 °C. This mixture was poured into a separatory funnel containing CH_2Cl_2 (30 mL) and H_2O (15 mL), the phases were separated, and the aqueous layer was back-extracted with CH_2Cl_2 (35 mL). The combined organic extracts were washed with H_2O (50 mL) and brine (50 mL), dried with Na_2SO_4, and concentrated. Flash chromatography with 15−25% EtOAc/hexanes provided the pure product as a colorless oil in 93% yield (1.95 g, 8.9 mmol). Product ratios were determined by HPLC with a Chiralcel OD-H column (95:5 hexanes/EtOAc; 1.0 mL/min): anti enantiomers $t_r = 8.5$ min, 9.4 min; *syn*-(2*R*,3*R*) $t_r = 11.8$ min; *syn*-(2*S*,3*S*) $t_r = 12.8$ min; 98:2 syn:anti; 98% syn ee.

Preparation of (2*S*,3*S*)-*tert*-Butyl 3-Hydroxy-3-methoxycarbonyl-2-isobutylbutanethioate (Table 9, Entry 9). This compound was prepared according to the general procedure (1.5 mL of CH_2Cl_2; 2 days at −78 °C) employing the silylketene acetal derived from *tert*-butyl 4-methylpentanethioate as a 90:10 mixture of *Z*:*E* isomers (130 mg, 0.50 mmol) and methyl pyruvate (45 μL, 0.50 mmol) to provide the pure product as a colorless oil in 58% yield (83 mg, 0.29 mmol) after flash chromatography with 2.5% Et_2O/CH_2Cl_2. Product ratios were determined by HPLC with a Chiralcel OD-H column (98.5:1.5 hexanes/2-propanol; 1.0 mL/min): anti enantiomers $t_r = 5.2$ min; *syn*-(2*R*,3*R*) $t_r = 5.7$ min; *syn*-(2*S*,3*S*) $t_r = 6.4$ min; 93:7 syn:anti; 97% syn ee; $[\alpha]^{rt}_D$ +34.7 (*c* 4.1, $CHCl_3$); IR (neat) 3508, 2958, 2870, 1735, 1682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 3.46 (br s, 1H), 2.93 (dd, $J = 2.9$, 11.4 Hz, 1H), 1.91 (ddd, $J = 3.8$, 11.4, 13.7 Hz, 1H, 1.54 (m, 1H), 1.45 (s, 3H), 1.44 (s, 9H), 1.00 (ddd, $J = 2.9$, 10.2, 13.7 Hz, 1H), 0.89 (d, $J = 6.5$ Hz, 3H), 0.82 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 175.1, 76.3, 58.8, 52.8, 48.9, 37.6, 29.5, 25.7, 24.7, 23.8, 21.3; LRMS (CI/NH_3) *m*/*z* 291 $(MH)^+$, 308 $(M + NH_4)^+$; HRMS (CI/NH_3) exact mass calcd for $(C_{14}H_{26}O_4S + NH_4)^+$ requires *m*/*z* 308.1896, found *m*/*z* 308.1901.

Preparation of (2*S*,3*S*)-Ethyl 3-Hydroxy-3-methoxycarbonyl-2-isobutylbutanethioate (Table 9, Entry 10) from the (*Z*)-Silylketene Acetal Isomer. This compound was prepared according to the general procedure (1.5 mL of CH_2Cl_2; 2 days at −78 °C) employing the silylketene acetal derived from ethyl 4-methylpentanethioate as a 90:10 mixture of *Z*:*E* isomers (150 μL, 0.60 mmol) and methyl pyruvate (45 μL, 0.50 mmol) to provide the pure product as a colorless oil in

88% yield (115 mg, 0.44 mmol) after flash chromatography with 10−20% EtOAc/hexane. Product diastereomer ratios were determined from integration of the ^{1}H NMR spectra. For determination of enantioselectivty, a small portion was purified by preparative TLC to remove the anti diastereomer, and the resultant material was analyzed by HPLC using a Chiralcel OD-H column (99:1 hexanes/2-propanol; 1.0 mL/min): *syn*-(2*R*,3*R*) $t_r = 8.7$ min; *syn*-(2*S*,3*S*) $t_r = 10.4$ min; 90:10 syn:anti; 93% syn ee; $[\alpha]^{rt}_D$ +21.2 (*c* 0.85, $CHCl_3$); IR (neat) 3507, 2957, 2872, 1734, 1685 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 3.45 (br s, 1H), 3.04 (dd, $J = 2.9$, 11.5 Hz, 1H), 2.91 (q, $J = 7.5$ Hz, 2H), 1.94 (ddd, $J = 3.7$, 11.5, 13.5 Hz, 1H), 1.53 (m, 1H), 1.45 (s, 3H), 1.24 (t, $J = 7.5$ Hz, 3H), 1.05 (ddd, $J = 2.9$, 10.4, 13.5 Hz, 1H), 0.91 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 175.3, 76.1, 59.2, 52.9, 37.7, 25.8, 24.7, 23.8, 23.7, 21.3, 14.5; LRMS (CI/NH_3) *m*/*z* 263 $(MH)^+$, 280 $(M + NH_4)^+$; HRMS (CI/NH_3) exact mass calcd for $(C_{12}H_{22}O_4S + NH_4)^+$ requires *m*/*z* 280.1583, found *m*/*z* 280.1586.

Preparation of (2*S*,3*S*)-*tert*-Butyl 3-Hydroxy-3-methoxycarbonyl-2-isopropylbutanethioate (Table 9, Entry 11). This compound was prepared according to the general procedure (1.5 mL of CH_2Cl_2) employing the silylketene acetal derived from *tert*-butyl 3-methylbutanethioate as a 90:10 mixture of *Z*:*E* isomers (148 mg, 0.60 mmol) and methyl pyruvate (45 μL, 0.50 mmol), except that the reaction required 2 days at room temperature to achieve complete conversion. Analysis of the unpurified product indicated a 67:33 syn:anti (97% syn ee) product mixture. Flash chromatography with 10−20% EtOAc/hexanes provided the syn adduct in 51% yield (71 mg, 0.26 mmol) as well as the anti adduct in 20% yield (27 mg, 0.10 mmol), resulting in a 71% combined yield. HPLC analysis indicated that the purified syn adduct was obtained with 98:2 syn:anti diastereoselectivity and 97% syn ee; $[\alpha]^{rt}_D$ +42.4 (*c* 2.9, $CHCl_3$). Product ratios were determined by HPLC with a Chiralcel OD-H column (99:1 hexanes/2-propanol; 1.0 mL/min): anti enantiomers $t_r = 4.6$ min; *syn*-(2*R*,3*R*) $t_r = 5.9$ min; *syn*-(2*S*,3*S*) $t_r = 8.1$ min. Syn isomer: mp 69.5−70.0 °C; IR (neat) 3685, 3526, 2967, 2875, 1750, 1731, 1680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.37 (br s, 1H), 2.78 (d, $J = 7.5$ Hz, 1H), 2.10 (octet, $J = 6.9$ Hz, 1H), 1.44 (s, 9H), 1.43 (s, 3H), 0.95 (d, $J = 6.8$ Hz, 3H), 0.89 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8, 175.4, 75.8, 65.4, 52.6, 49.0, 29.4, 28.4, 26.7, 21.8, 21.0; LRMS (CI/NH_3) *m*/*z* 277 $(MH)^+$, 294 $(M + NH_4)^+$; HRMS (CI/NH_3) exact mass calcd for $(C_{13}H_{24}O_4S + NH_4)^+$ requires *m*/*z* 294.1739, found *m*/*z* 294.1749.

Preparation of (2*S*,3*S*)-Ethyl 3-Hydroxy-3-methoxycarbonyl-2-isopropylbutanethioate (Table 9, Entry 12). This compound was prepared according to the general procedure (1.5 mL of CH_2Cl_2; 12 h at −50 °C) employing the silylketene acetal derived from *tert*-butyl 3-methylbutanethioate as a 90:10 mixture of *Z*:*E* isomers (156 μL, 0.60 mmol) and methyl pyruvate (45 μL, 0.50 mmol) to provide the pure product as a colorless oil in 80% yield (100 mg, 0.40 mmol) after flash chromatography with 10−20% EtOAc/hexanes: 90:10 syn:anti; 99% syn ee; $[\alpha]^{rt}_D$ +45.9° (*c* 1.2, $CHCl_3$). Product ratios were determined by HPLC with a Chiralcel OD-H column (98:2 hexanes/^{i}PrOH; 1.0 mL/min): anti enantiomers $t_r = 5.6$, 6.0 min; *syn*-diasteromers $t_r = 7.5$, 9.7 min. Syn isomer: IR (neat) 3497, 2969, 2875, 1733, 1687 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.46 (br s, 1H), 2.93 (m, 3H), 2.15 (app sextet, $J = 6.8$ Hz, 1H), 1.44 (s, 3H, Me), 1.28 (t, $J = 7.4$ Hz, 3H), 0.97 (d, $J = 6.8$ Hz, 3H), 0.96 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 175.5, 75.6, 65.8, 52.7, 28.4, 26.7, 23.7, 21.9, 21.0, 14.5; LRMS (CI/NH_3) *m*/*z* 249 $(MH)^+$, 266 $(M + NH_4)^+$; HRMS (CI/NH_3) exact mass calcd for $(C_{11}H_{20}O_4S + NH_4)^+$ requires *m*/*z* 266.1426, found *m*/*z* 266.1432.

Preparation of (1′*R*,4*S*)-4-(1′-Hydroxy-1′-methoxycarbonylethyl)-5-oxacyclopent-2-enone (18, Eq 22). Compound **18** was prepared according to the general procedure (1.5 mL of THF; 2 h at −78 °C) employing 2-trimethylsiloxyfuran (101 μL, 0.60 mmol) and methyl pyruvate (45 μL, 0.50 mmol). This material was extremely soluble in water such that the normal aqueous workup procedure resulted in low yield (25%). Therefore, a modified procedure was employed in which the silyl ether was cleaved using 0.2 M HCl in MeOH (4 mL). After 15 min, the reaction mixture was concentrated by rotary evaporation and applied directly to a flash chromatography column. After chromatography with 60% EtOAc/hexanes, the pure product was obtained as a colorless oil in 100% yield (94 mg, 0.50 mmol). Product ratios were determined by HPLC with a Chiralcel AD column (90:10 hexanes/2-propanol; 1.0 mL/min): *anti*-(1′*S*,4*R*) $t_r = 13.2$ min; *anti*-(1′*R*,4*S*) $t_r = 14.0$ min; syn enantiomers $t_r = 19.1$, 25.4 min; 95:5 *anti*:*syn*; 99% anti ee; $[\alpha]^{rt}_D$ −87.8 (*c* 5.9, $CHCl_3$). Anti isomer: IR (CH_2Cl_2 solution) 3686, 3535, 2958, 1787, 1761, 1741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, $J = 1.5$, 5.8 Hz, 1H), 6.22 (dd, $J = 2.0$, 5.8 Hz, 1H), 5.10 (t, $J = 1.8$ Hz, 1H), 3.83 (s, 3H), 3.28 (br s, 1H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 172.2, 152.2, 123.4, 86.0, 75.2, 53.4, 21.4; LRMS (CI/NH_3) *m*/*z* 204 $(M + NH_4)^+$; HRMS (CI/NH_3) exact mass calcd for $(C_8H_{10}O_5 + NH_4)^+$ requires *m*/*z* 204.0872 found *m*/*z* 204.0875.

Preparation of (2*S*,3*S*)-*tert*-Butyl 2,3-Dimethyl-3-hydroxy-4-oxohexanethioate (21, Eq 27). Compound **21** was prepared according to the general procedure (2.0 mL of CH_2Cl_2; −78 °C) the (*Z*)-silylketene acetal derived from *tert*-butyl thiopropionate (125 μL, 0.50 mmol) and 2,3-pentanedione (52 μL, 0.50 mmol) to provide the pure product as a clear oil in 85% yield (106 mg, 0.43 mmol) after flash chromatography with 10% EtOAc/hexanes. The product ratios were determined as follows. Regioisomer and diastereomer ratios were determined by GC with a Chiraldex BDA column (80 °C, 0.5 °C/min gradient, 20 psi): anti ethyl ketone adducts (2 compounds) $t_r = 44.5$ min; syn and anti methyl ketone adducts (4 compounds) $t_r = 48.3$ min; syn ethyl ketone adducts (2 compounds) $t_r = 56.0$ min. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (99.3:0.7 hexanes/EtOAc; 0.5 mL/min): syn methyl ketone adduct enantiomers $t_r = 12.5$, 13.5 min; syn ethyl ketone adduct (*R*) enantiomer $t_r = 14.5$ min; syn ethyl ketone adduct (*S*) enantiomer $t_r = 15.1$ min; 98:2 ethyl ketone adducts:methyl ketone adducts, 93:7 syn:anti; 97% syn ee; $[\alpha]^{rt}_D$ +89.4 (*c* 2.0, CH_2Cl_2); IR (neat) 3500, 2975, 1718, 1652 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 1H), 2.98 (q, $J = 7.1$ Hz, 1H), 2.63 (m, 2H, 1.45 (s, 9H), 1.30 (s, 3H), 1.07 (d, $J = 7.1$ Hz, 3H), 1.01 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.4, 205.3, 80.4, 53.7, 48.7, 30.8, 29.5, 25.1, 13.4, 7.3; LRMS (CI/NH_3) *m*/*z* 247 $(MH)^+$, 264 $(M + NH_4)^+$; HRMS (CI/NH_3) exact mass calcd for $(C_{12}H_{22}O_3S + H)^+$ requires *m*/*z* 247.1368, found *m*/*z* 247.1378.

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Supporting Information Available: General experimental information; absolute and relative stereochemical proofs; minor diastereomer characterization date; role of solvent on relative rates of addition; silyl crossover experiments; EPR spectra; X-ray crystallographic data; and PM3 calculation results (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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