

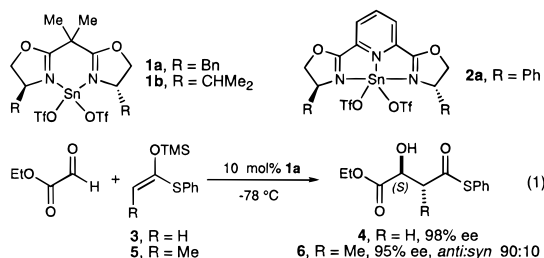
## C<sub>2</sub>-Symmetric Tin(II) Complexes as Chiral Lewis Acids. Catalytic Enantioselective *Anti* Aldol Additions of Enolsilanes to Glyoxylate and Pyruvate Esters

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Stannous triflate–diamine complexes are effective organizational centers for Lewis acid promoted aldol reactions.<sup>1</sup> However, the documented difficulties in rendering these processes catalytic in metal complex appear to contradict the established fact that Sn(II) complexes are kinetically labile toward ligand substitution.<sup>2</sup> In this communication we demonstrate that ligand architecture can play an important role in the design of Sn(II)-based chiral Lewis acidic complexes. Specifically, the Lewis acidic complexes **1** and **2** derived from Sn(OTf)<sub>2</sub><sup>3</sup> and bidentate bis(oxazoline)<sup>4</sup> and tridentate pyridyl-bis(oxazoline)<sup>5</sup> ligands<sup>6</sup> are efficient *anti*-aldol catalysts for the enantioselective addition of enolsilanes to 1,2-dicarbonyl compounds. These ligand–metal complexes exhibit efficient turnover in the catalytic cycle and may be employed in amounts as low as 2 mol %.



The efficiency of complexes **1** and **2** in catalyzing the addition of enolsilanes to glyoxylate esters (eq 1) was examined.<sup>7</sup> In analogy to related Cu(II) studies,<sup>8</sup> it was assumed that chelate organization between the catalyst and carbonyl-containing reactant might provide a stereoselective process with this and related substrates. A survey of ligand architecture for the addition of silylketene acetal **3** to ethyl glyoxylate (eq 1, R = H) revealed that several [Sn(box)](OTf)<sub>2</sub> complexes **1** (10 mol %, –78 °C, 5 min) efficiently catalyze the formation of the malate diester **4** in good yield in greater than 90% ee.<sup>9</sup> The

(1) (a) Kobayashi, S.; Horibe, M.; Saito, Y. *Tetrahedron* **1994**, *50*, 9629–42. (b) Kobayashi, S.; Uchiro, H.; Shiina, I.; Mukaiyama, T. *Tetrahedron* **1993**, *49*, 1761–72.

(2) Veith, M.; Recktenwald, O. *Topics in Current Chemistry, Organotin Compounds*; Springer: Berlin, 1982; Vol. 104, pp 1–58.

(3) Batchelor, R. J.; Ruddick, J. N. K.; Sams, J. R.; Auble, F. *Inorg. Chem.* **1977**, *16*, 1414–17.

(4) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726–8.

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

(6) Sn(OTf)<sub>2</sub> derived bis(oxazoline) and pyridyl-bis(oxazoline) complexes are denoted as [Sn(box)](OTf)<sub>2</sub> and [Sn(pybox)](OTf)<sub>2</sub>, respectively.

(7) Typically the catalysts were formed by stirring bis(oxazolonyl) (0.055 mmol) or bis(oxazolonyl)pyridyl ligands (0.055 mmol) with Sn(OTf)<sub>2</sub> (0.05 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.8 mL) for 1 h at room temperature to yield homogenous colorless solutions for box-derived complexes or homogenous yellow solutions for pybox-derived complexes.

(8) (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.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* In press.

(9) Enantioselectivities obtained with other [Sn(box)](OTf)<sub>2</sub> complexes: [Sn((S,S)-Ph-box)](OTf)<sub>2</sub> (91% ee), [Sn((S,S)-Pr-box)](OTf)<sub>2</sub> (93% ee). In contrast, the [Sn(pybox)](OTf)<sub>2</sub> complexes (**2**) proved to be ineffective catalysts for this reaction.

**Table 1.** Enantioselective Aldol Reactions between Ethyl Glyoxylate and Representative Silylketene Acetals (Eq 2)

entry	SR	R <sup>1</sup>	anti:syn	% ee <sup>a,b</sup>	% yield
1	SPh	H	--	98	90
2	SPh <sup>c</sup>	Me	90:10	95	87
3	SPh <sup>c</sup>	Et	92:8	95	90 <sup>d</sup>
4	SPh <sup>c</sup>	<sup>i</sup> Pr	93:7	95	72 <sup>d</sup>
5	SPh <sup>c</sup>	<sup>t</sup> Bu	92:8	98	88
6	S <sup>t</sup> Bu <sup>c</sup>	<sup>t</sup> Bu	96:4	96 <sup>e</sup>	83 <sup>d</sup>
7	SEt <sup>c</sup>	<sup>t</sup> Bu	92:8	92 <sup>e</sup>	83

<sup>a</sup> Product ratios determined by HPLC using a Chiralcel OD-H or AD column after hydrolysis of the product TMS ether (ref 10).

<sup>b</sup> Relative and absolute stereochemical assignments determined by independent synthesis (see Supporting Information). <sup>c</sup> Enolsilane geometry (Z), isomeric purity ≥95%. <sup>d</sup> Product configuration assigned by analogy. <sup>e</sup> This experiment was carried out with catalyst **1b** (10 mol %).

superior levels of asymmetric induction exhibited by [Sn((S,S)-Bn-box)](OTf)<sub>2</sub> (**1a**) which afforded (*S*)-**4** in 98% ee (10 mol % catalyst, CH<sub>2</sub>Cl<sub>2</sub>, –78 °C, 5 min, 99% yield) prompted us to select this catalyst for further exploration.<sup>10</sup> The addition of substituted (*Z*) silylketene acetal<sup>11</sup> **5** to ethyl glyoxylate (eq 1, R = Me) in the presence of **1a** provides the malate derivative (*S*)-**6**<sup>12</sup> in high enantioselectivity (95% ee), yield (87%), and *anti* reaction diastereoselection (90:10 *anti:syn*). To our knowledge, only one previous example of a chiral Lewis acid catalyzed *anti*-aldol reaction has been reported,<sup>13</sup> albeit with higher catalyst loadings and lower enantioselectivities. As such, further study into the generality of [Sn((S,S)-Bn-box)](OTf)<sub>2</sub> as an *anti* aldol catalyst was undertaken (Table 1).

From the results summarized in Table 1, both *anti* diastereoselection and reaction enantioselectivity (95–98% ee) are maintained for a range of alkyl-substituted silylketene acetals (entries 2–5, Me, Et, <sup>i</sup>Pr, <sup>t</sup>Bu). These data document a modest trend toward higher *anti* diastereoselection as the steric requirements of the enolsilane alkyl substituent increase. Although phenyl thioester-derived silylketene acetals are generally superior for additions to glyoxylate esters mediated by **1a**, substituted enolsilanes derived from ethyl and *tert*-butyl thioesters can also furnish *anti*-aldol adducts in high enantioselectivity (entries 6 and 7) (≥92:8 *anti:syn*, 92–96% ee) in the presence of [Sn((S,S)-<sup>i</sup>Pr-box)](OTf)<sub>2</sub> (**1b**). The preparative utility of this methodology has also been evaluated. The addition of silylketene acetal **3** to ethyl glyoxylate was performed on a 25-mmol scale utilizing complex **1a** (2 mol %) to afford (*S*)-**4** (94% ee, 90% yield).<sup>14</sup>

The capacity of complexes **1** and **2** to facilitate catalyst–substrate organization through presumed bidentate coordination was further evaluated with α-keto esters.<sup>15</sup> Ligand optimization in the addition of the substituted silylketene acetal **7** to methyl pyruvate indicated that both Sn(II)–box and –pybox complexes

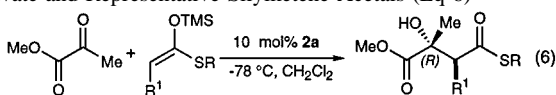
(10) The catalysts were prepared as described above, see ref 7. In a representative procedure the silylketene acetal (0.50 mmol) and ethyl glyoxylate (0.75 mmol) were added sequentially to a catalyst solution in CH<sub>2</sub>Cl<sub>2</sub> (0.8 mL, 0.05 mmol, 10 mol %) at –78 °C. After the reaction was complete (5 min–2 h), the mixture was filtered through silica with Et<sub>2</sub>O, and the silyl ether was hydrolyzed with 1 N HCl in THF (30 min, 25 °C) to yield the hydroxyester, which was purified by flash chromatography.

(11) For the addition to ethyl glyoxylate catalyzed by **1** and **2**, (*E*)-silylketene acetals were found to be less reactive and led to the formation of malate derivatives in lower yield and with diminished *anti* selectivity.

(12) 3-Alkyl malic acid derivatives may also be obtained through alkylation of the malate diester-derived enolate. Seebach, D.; Aebi, J.; Wasmuth, D. *Org. Synth.* **1984**, *63*, 109–120, and references cited therein.

(13) Parmee, E. R.; Hong, Y.; Tempkin, O.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 1729–32.

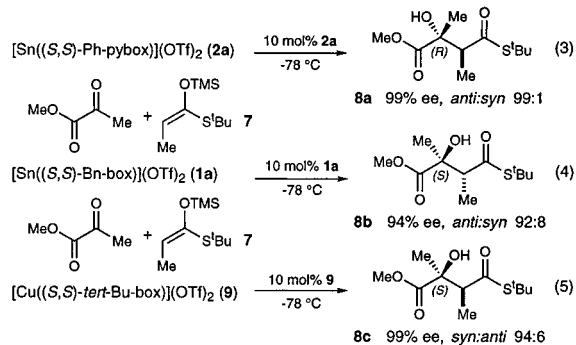
(14) When this preparative reaction was repeated with 10 mol % catalyst, the enantioselectivity was slightly higher (98% ee, 90% yield).

**Table 2.** Enantioselective Aldol Reactions between Methyl Pyruvate and Representative Silylketene Acetals (Eq 6)


entry	SR	R <sup>1</sup>	enolsilane geometry <sup>a</sup>	<i>anti:syn</i>	% ee <sup>b,c</sup>	% yield
1	S <sup>t</sup> Bu	Me	( <i>Z</i> )	99:1	99	94
2	S <sup>t</sup> Bu	Me	( <i>E</i> )	99:1	96	84
3	S <sup>t</sup> Bu	Et	( <i>Z</i> )	98:2	97	84 <sup>d</sup>
4	S <sup>t</sup> Bu	<sup>i</sup> Bu	( <i>Z</i> )	99:1	99	81 <sup>d</sup>
5	SEt	Me	( <i>Z</i> )	95:5	92	91
6	SEt	Et	( <i>Z</i> )	99:1	97	94 <sup>d</sup>
7	SEt	<sup>i</sup> Bu	( <i>Z</i> )	99:1	97	76 <sup>d</sup>

<sup>a</sup> Enolsilane isomeric purity  $\geq 95\%$ . <sup>b</sup> Product ratios determined by HPLC using a Chiralcel OD-H column after hydrolysis of the product TMS ether (ref 10). <sup>c</sup> Relative and absolute stereochemical assignments determined by independent synthesis (see Supporting Information). <sup>d</sup> Product configuration assigned by analogy.

effectively catalyze the formation of functionalized succinates **8** with a high degree of stereochemical control (eqs 3 and 4). The exceptional levels of stereocontrol displayed by (*S,S*)-phenyl-pybox complex **2a** to afford (*R*)-**8a** as a 99:1 *anti:syn* mixture in 99% ee and 84% yield (eq 3) established this complex as the catalyst for further exploration.<sup>16</sup> Upon optimization, 2 mol % of **2a** at 1.3 M concentration of silylketene acetal and pyruvate ester was found to catalyze the reaction in 24 h without a decrease in yield or stereoselectivity. An enantioselectivity/temperature profile conducted with complex **2a** (eq 3) documents that Sn(II)-pybox catalysts retain stereochemical control at elevated temperatures ( $-78$  °C, 99:1 *anti:syn*, 99% ee;  $0$  °C, 95:5 *anti:syn*, 86% ee). It is noteworthy that the *anti* selectivity observed for this reaction serves to complement the Cu(II)-box mediated addition of substituted enolsilanes to pyruvate esters in which *syn* diastereoselection is observed (eq 5).<sup>8b</sup>



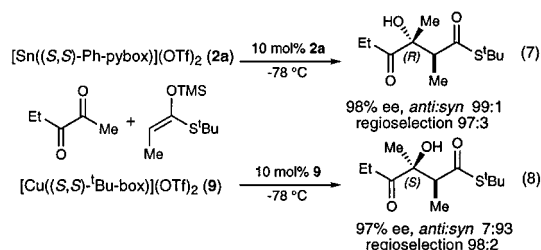
The catalyzed addition to pyruvates is also general with respect to the silylketene acetal structure (Table 2, eq 6). Both (*E*) and (*Z*) isomers of the silylketene acetal **7** (entries 1 and 2) react in a stereoconvergent manner providing the substituted succinate derivative **8a** with excellent overall selectivity (99:1 *anti:syn*,  $\geq 96\%$  ee). Variation in the size of the enolsilane alkyl substituent is possible without significant loss in stereoselectivity (entries 2–4,  $>98:2$  *anti:syn*,  $>97\%$  ee). Finally, high levels

(15) Evidence for bidentate chelation in these reactions is largely circumstantial. As electrophiles, pyruvate esters and simple aldehydes have comparable reactivities. In the presence of catalyst **2a**, however, addition of enolsilanes to pyruvate esters is complete within 4 h at  $-78$  °C, while the use of hydrocinnamaldehyde leads to no reaction at  $-78$  °C and only 50% completion after 72 h at  $-30$  °C (70% ee).

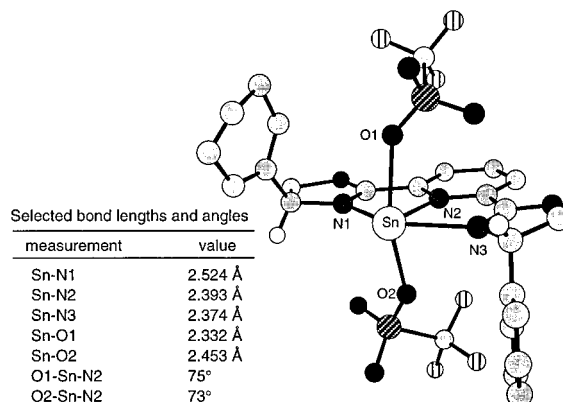
(16) The catalysts were prepared as described above, see ref 7. In a representative procedure methyl pyruvate (0.50 mmol) and the silylketene acetal (0.6 mmol) were added sequentially to a catalyst solution in  $\text{CH}_2\text{Cl}_2$  (0.8 mL, 0.05 mmol, 10 mol %) at  $-78$  °C. After the reaction was complete (4–24 h), the mixture was filtered through silica with  $\text{Et}_2\text{O}$ , and the silyl ether was hydrolyzed with 1 N HCl in THF (1 h,  $25$  °C) to yield the hydroxyester, which was purified by flash chromatography.

of diastereo- and enantiocontrol are observed in the addition of silylketene acetals derived from ethyl thioesters (entries 5–7,  $\geq 95:5$  *anti:syn*,  $>92\%$  ee).

A further illustration of the capacity of Sn(II) complexes to achieve high levels of catalyst-substrate organization is presented in the addition of enolsilanes to unsymmetrical vicinal diketones (eq 7). The principal issue in this reaction is that of catalyst-controlled discrimination of methyl- and ethyl-substituted carbonyls toward nucleophilic attack. In contrast to the modest bias for addition to the  $\text{MeCO}$ -moiety (1.4:1) when catalyzed by  $\text{TiCl}_4$  ( $-78$  °C,  $\text{CH}_2\text{Cl}_2$ ), the addition of the (*Z*) silylketene acetal **7** to 2,3-pentanedione catalyzed by **2a** proceeds with excellent regioselectivity (97:3), diastereoselectivity (99:1) and enantioselectivity (98% ee). In comparison, the same reaction catalyzed by  $[\text{Cu}((S,S)\text{-}t\text{-Bu-box})](\text{OTf})_2$  (**9**) proceeds with comparable stereoselection to afford the diastereoisomeric adduct (regioselectivity 97:3, *syn:anti* 93:7, 97% ee) (eq 8).<sup>8b</sup>



The X-ray structure of  $[\text{Sn}((S,S)\text{-Ph-pybox})](\text{OTf})_2$  (**2a**) is presented in Figure 1. The crystallographic data for catalyst **2a** reveals a  $\psi$ -octahedral geometry with distortion of the oxazoline and triflate ligands away from the stereochemically active Sn(II) lone pair. Insight into the solution structure(s) of the ligand-metal species was provided by electrospray ionization (ESI) studies. Positive mode ESI reveals the presence of  $[\text{Sn}(\text{Ph-pybox})_2](2+)$  and  $[\text{Sn}(\text{Ph-pybox})](\text{OTf})(1+)$ , while in the negative mode, an abundance of triflate ion is observed. These experiments further highlight the kinetic lability of bisoxazoline derived Sn(II) complexes toward ligand substitution. Studies to address the coordination chemistry of related complexes will be forthcoming.

**Figure 1.** X-ray structure of  $[\text{Sn}(\text{Ph-Pybox})](\text{OTf})_2$  (**2a**).

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**Supporting Information Available:** Experimental procedures, spectral data for all compounds, stereochemical proofs, and X-ray crystallographic data (16 pages). See any masthead page for ordering and Internet access instructions.