ORGANIC LETTERS

2002
Vol. 4, No. 20
3375−3378

C_2-Symmetric Sc(III)-Complexes as Chiral Lewis Acids. Catalytic Enantioselective Aldol Additions to Glyoxylate Esters

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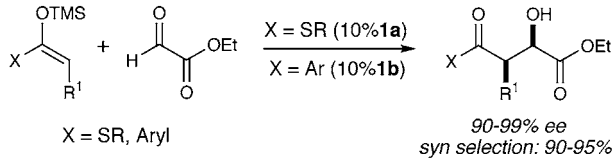
Received July 9, 2002

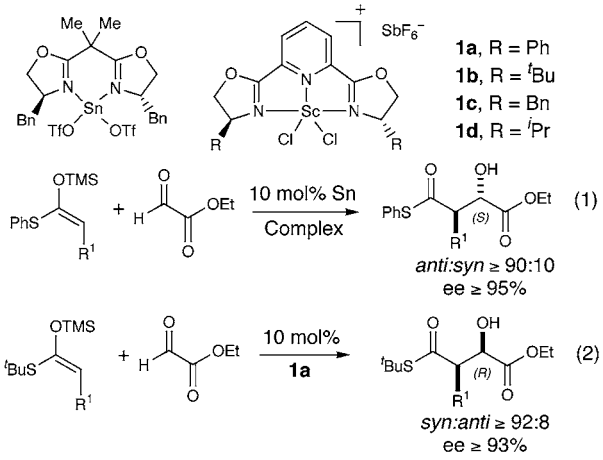
ABSTRACT



Cationic Lewis acid complexes [Sc(pyridyl-bis(oxazolinyl)](Cl$_2$)SbF$_6$ 1a and 1b catalyze aldol reactions with ethyl glyoxylate with enantioselectivities ranging from 90 to 99% ee and syn reaction diastereoselections ranging from 90:10 to 95:5.

Our laboratory has recently described the use of cationic bis(oxazoline)Cu(II),[1] bis(oxazoline)Zn(II),[2] and bis(oxazoline)-Sn(II)[3] complexes as Lewis acid catalysts for highly enantioselective carbonyl addition reactions.[4] In particular, the Sn(II) complexes derived from bis(oxazolinyl) and pyridylbis(oxazolinyl) ligands, hereafter referred to as box and pybox, respectively, are effective catalysts for the anti-selective Mukaiyama aldol reaction with enolsilanes and pyruvate or glyoxylate electrophiles (eq 1). However, the corresponding syn aldol process with glyoxylate esters was not selectively mediated by either the [Cu(II)-box] or [Zn-(II)-box] complexes. This Letter documents the utility of cationic complexes [Sc((*S*,*S*))-Ph-pybox)](Cl$_2$)SbF$_6$ (**1a**) and [Sc((*S*,*S*)-^{t}Bu-pybox)](Cl$_2$)SbF$_6$ (**1b**) as Lewis acid catalysts in the syn-selective aldol addition reactions between enolsilanes and ethyl glyoxylate (eq 2).[5]

It was anticipated that the Sc(III)−ligand complexes, by virtue of a higher formal positive charge, might be more active Lewis acid catalysts than their Cu(II), Zn(II), or Sn-(II) analogues. In analogy to our Cu(II) studies,[6] it was anticipated that chelate organization between the catalyst and the reactive carbonyl might provide a stereoselective process with glyoxylate and related substrates. Herein, we describe



an efficient approach to the synthesis of malate derivatives as well as aryl-substituted α-hydroxy-γ-ketoesters using Sc-(III)-pybox catalysts. These metal−ligand complexes exhibit efficient turnover within the catalytic cycle and can be utilized in amounts as low as 5 mol %.

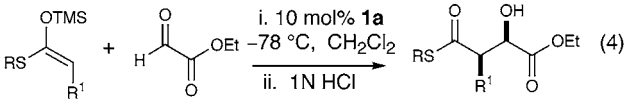
Our initial studies began with an evaluation of the [Sc-((*S*,*S*)-Ph-pybox)](OTf)$_3$ complex, which was known to be a selective catalyst for additions to ethyl glyoxylate.[5]

10.1021/ol026488l CCC: $22.00
Published on Web 09/07/2002

However, this complex proved to be only moderately selective in additions of thiosilylketene acetals to ethyl glyoxylate. We next explored the counterion variable in an effort to obtain a more selective aldol process. The cationic [Sc-pybox]$(Cl)_2^+$ complexes (**1a**−**d**), formed in situ by treatment of the [Sc-pybox]$(Cl)_3$ complexes with $AgSbF_6$ (1.0 equiv), were initially evaluated as catalysts for the enantioselective addition of thiosilylketene acetals to ethyl glyoxylate. For the [Sc-pybox]$(Cl)_2^+$ complexes, use of the thiosilylketene acetal derived from *tert*-butyl thioacetate produced the (*R*)-malate derivatives (**3**, eq 3) in good yield and with moderate to high levels of enantioselection.

Of the complexes surveyed, the phenyl-pybox-derived catalyst **1a** provided superior levels of asymmetric induction,[7] affording diester **3a** in 90% ee (10 mol % catalyst, 3 h, 92% yield). The addition of (*Z*)-thiosilylketene **2b** to ethyl gloxylate (eq 3, R^1 = Me) in the presence of **1a** afforded aldol product **3b** in high enantioselectivity (95% ee), yield (92%), and syn diastereoselection (dr 92:8). The scope of this aldol process is summarized in Table 1 (eq 4).

Table 1. Scandium-Catalyzed Glyoxylate Aldol Reaction



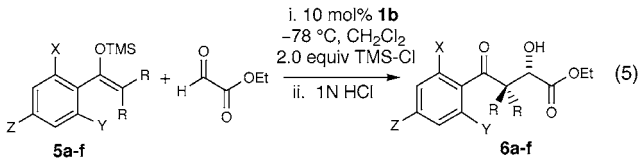
entry	SR	R^1	syn:anti	% ee[a]	% yield
1	S^{t}Bu	H		90[b]	92 (**3a**)
2	S^{t}Bu[c]	Me	92:8	95[b]	93 (**3b**)
3	S^{t}Bu[c]	^{i}Pr	95:5	99[d]	90 (**3c**)
4	S^{t}Bu[c]	^{i}Bu	93:7	93[d]	94 (**3d**)
5	SPh[c]	Et	92:8	95[d]	90 (**3e**)
6	SEt[c]	OBn	92:8	95[d]	92 (**3f**)
7[e]	S^{t}Bu[c]	Me	92:8	93	90 (**3a**)

[a] Product ratios determined by HPLC using Chiracel OD-H or AD columns after hydrolysis of the product TMS ether. [b] Relative and absolute stereochemical assignments determined by independent synthesis (see Supporting Information). [c] (*Z*)-Enolsilane geometry, isomeric purity > 95%. [d] Product configuration assigned by analogy. [e] Catalyst **1a** (5 mol %).

Both the syn diastereoselection (dr ≥ 92:8) and reaction enantioselectivity (90−99% ee) are maintained for a range of alkyl- and alkoxy-substituted thiosilylketene acetals (entries 2−6). The reaction performed equally well with a range of thioesters (entries 2, 5, and 6). A particularly noteworthy example is the addition of the benzyloxy-substituted thiosilylketene acetal (entry 6), which furnished the fully differentiated tartrate (dr 92:8). To demonstrate the preparative utility of this syn aldol process, the addition of the methyl-substituted thiosilylketene acetal (**2b**, RS = S^{t}Bu, R^1 = Me) was conducted with 5 mol % catalyst loading to afford the (*R*,*R*)-malate ester (**3b**, RS = S^{t}Bu, R^1 = Me) in 93% ee (entry 7, 90% yield, dr 92:8, 10 mmol scale). For all the cases examined, the (*Z*)-thiosilylketene acetal isomer was essential for obtaining high levels of diastereo- and enantioselection. The corresponding (E)-isomers afforded significantly lower levels of diastereoselection.[8] Upon optimization of the catalyst system, 5 mol % **1a** at 1.0 M concentration of the thiosilylketene acetal **2b** was found to catalyze the reaction with ethyl glyoxylate in 10 h with high levels of stereoselection and yield (entry 7). A temperature−enantioselectivity profile, conducted with complex **1a**, established that the catalyst retains stereochemical control at elevated temperatures (−78 °C, dr 92:8, 95% ee; −10 °C, dr 92:8, 95% ee). It is especially noteworthy that the syn selectivity observed for the aldol adducts in Table 1 serves to complement *both* the relative and absolute stereochemistry observed with the [Sn((*S*,*S*)-Bn-box)]$(OTf)_2$ catalyst (**4**),[3] which affords the anti aldol products with the (S) configuration at the hydroxy-bearing stereocenter (eqs 1, 2).

In an effort to expand the scope of the glyoxylate aldol process, enolsilane nucleophiles derived from aryl ketones were next investigated. The reaction of ethyl glyoxylate with the enolsilane of isobutyrophenone was chosen to optimize the reaction. A survey of ligands revealed that the [Sc((*S*,*S*)-^{t}Bu-pybox)]$(Cl_2)SbF_6$ complex (**1b**) provided the α-hydroxy-γ-ketoesters with excellent levels of stereocontrol. The scope of enolsilane additions to ethyl glyoxylate is shown in Table 2 (eq 5). The high enantioselectivity of the process (91−99% ee) is maintained for a range of both acyclic and cyclic disubstituted enolsilanes as well as unsubstituted enolsilane nucleophiles.

Table 2. Aryl Enolsilane Additions to Ethyl Glyoxylate



entry	R	X	Y	Z	% ee[a]	% yield
1	Me	H	H	H	95[b]	85 (**6a**)
2	Me	H	H	F	95[d]	85 (**6b**)
3	$(CH_2)_5$	H	H	H	97[d]	80 (**6c**)
4	$(CH_2)_4$	H	H	H	98[b]	81 (**6d**)
5	H	Cl	Cl	H	96[c]	96 (**6e**)
6	H	Br	H	H	91[d]	91 (**6f**)

[a] Enantiomeric excess determined by HPLC using Chiracel OD-H or AD columns after hydrolysis of the product TMS ether. [b] Absolute stereochemistry determined by Mosher analysis (see Supporting Information). [c] Absolute stereochemistry determined by X-ray analysis (see Supporting Information). [d] Product configuration assigned by analogy.

Our initial studies focused on the use of the isobutyrophenone-derived enolsilane **5a** as its larger effective steric bulk provided high levels of induction in the additions to ethyl

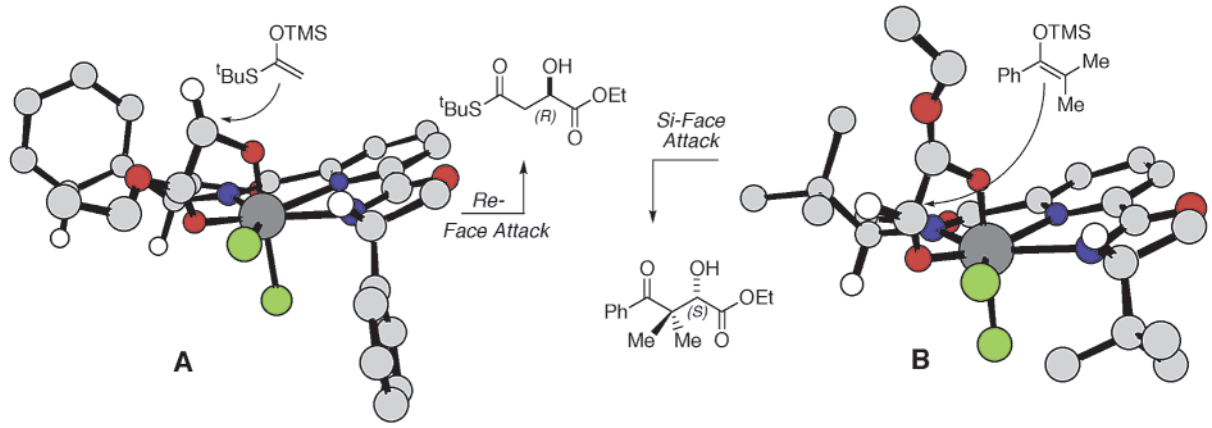


Figure 1. Stereochemical rationale for enolsilane additions to ethyl glyoxylate catalyzed by Sc complexes **1a** and **1b**.[10]

glyoxylate. In additions of these enolsilane nucleophiles, the use of 2.0 equiv of chlorotrimethylsilane was essential to facilitate catalyst turnover. The use of a para-substituted isobutyrophenone-derived enolsilane (entry 2) as well as cyclic variants of the disubstituted enolsilanes (entries 3 and 4) performed equally well in terms of both yield and enantioselection. Initial attempts with enolsilanes derived from acetophenone provided low levels of induction in the aldol reaction with catalyst **1b**, presumably due to the more planar nature of the enolsilane nucleophile.[9] In an attempt to test this hypothesis and expand the methodology to include acetophenone-derived enolsilanes, ortho-substituted enolsilanes (entries 5 and 6) were surveyed.

It was anticipated that ortho substitution would expand the dihedral angle between the aryl ring and the olefinic moiety, thereby effectively increasing the steric bulk of the nucleophile and affording a more selective aldol addition. Gratifyingly, these ortho-substituted enolsilanes afford the α-hydroxy-γ-ketoesters with high levels of enantioselectivity (entries 5 and 6) comparable to the values observed with the isobutyrophenone-derived enolsilanes. An X-ray crystallographic analysis of adduct **6e** confirmed the (S) configuration of the glyoxylate adduct (see Supporting Information).

Of particular note, the enolsilane additions mediated by catalyst **1b** afforded the opposite sense of induction from that obtained with catalyst **1a** using the thiosilylketene acetal nucleophiles (Table 1). In all cases examined in Table 2, the arylenolsilane additions to ethyl glyoxylate afford the complementary (*S*)-α-hydroxy-γ-ketoesters with high levels of enantiocontrol.

The stereochemical course of both the thiosilylketene acetal and arylenolsilane additions to ethyl glyoxylate can be rationalized by the model[10] shown in Figure 1. Models **A** and **B** represent the minimized transition state structures of complexes **1a** and **1b** docked with ethyl glyoxylate, respectively.[11] In model **A**, the aldehyde functionality is bound in the apical position, thereby favoring addition to the re-face of the aldehyde carbonyl as the si-face is effectively shielded by a phenyl group of the pybox ligand. In model **B**, the aldehyde moiety is bound in the equatorial position, thereby favoring addition to the si-face of the aldehyde carbonyl as the re-face is effectively blocked by the *tert*-butyl group of the pybox ligand. In each of these representations, the binding of the aldehyde carbonyl in a single position (i.e., apical in model **A**, equatorial in model **B**) during the addition of the nucleophile is necessary to explain the high levels of enantioselectivity observed for each of the glyoxylate additions. Steric factors within the chiral pocket of the scandium-catalyst may explain the preference for the location of the aldehyde carbonyl in the complex. Specifically, the reversal of binding preference for the aldehyde moiety in complexes **1a** and **1b** may be a result of the steric environment of the ligand architecture, which

(1) Evans, D. A.; Rovis, T.; Johnson, J. S. *Pure Appl. Chem.* **1999**, *71*, 1407−1415.

(2) Evans, D. A.; Kozlowski, M. C.; Tedrow, J. S. *Tetrahedron Lett.* **1996**, *37*, 7481−7484.

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

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

(5) Evans, D. A.; Sweeney, Z. K.; Rovis, T.; Tedrow, J. S. *J. Am. Chem. Soc.* **2001**, *123*, 12095−12096. For a syn-aldol, cf.: Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1994**, *116*, 4077−4078.

(6) (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.* **1997**, *119*, 7893−7894.

(7) Enantioselectivities obtained with other $[ScCl_2(pybox)]SbF_6$ complexes: **1b** (11% ee), **1c** (50% ee), **1d** (40% ee).

(8) For the addition to ethyl glyoxylate catalyzed by **1a**, the corresponding (*E*)-thiosilylketene acetals led to the formation of the malate products in lower yields and syn selectivity. For example, the reaction of (*E*)-**2b** afforded **3b** (80% ee, dr 1.4:1) and (*E*)-**2c** afforded **3c** (78% ee, dr 1:1).

(9) The trimethylsilyl enolsilane derived from acetophenone afforded the aldol product in 11% ee using the conditions in Table 2.

(10) This model was generated from the pentagonal-bipyramidal crystal structure of the Sc[Ph-pybox(H_2O)]($OTf)_3$ complex (ref 5) by the following procedure. Coordinates for the Sc[Ph-pybox(H_2O)]($OTf)_3$ complex were input into Chem 3D Pro; the vicinal triflates were removed and replaced with chloride ions, and the remaining triflate and bound water were replaced with ethyl glyoxylate, which was docked onto the Sc-center. The ligand−Sc bond lengths were held constant and the molecular energy of the structure minimized.

(11) These structures were subjected to a MM2 transition state minimization using Chem 3D Pro (Version 5.0). In each model, an apical or equatorial binding of the aldehyde carbonyl was minimized separately with the lower energy structure shown.

directs coordination of the ester group to the less sterically demanding position. A qualitative transition state model for the diastereoselection of the thiosilylketene acetal additions to ethyl glyoxylate is provided in Figure 2.

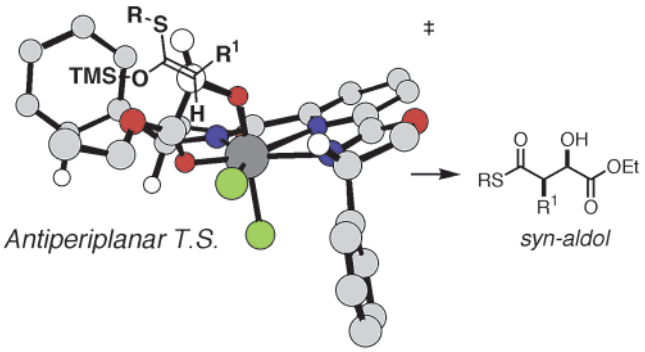


Figure 2. Transition state model for the thiosilylketene acetal additions to ethyl glyoxylate.

The observed syn stereoselection is consistent with an antiperiplanar transition state, which minimizes the steric interactions between the substituent (R^1) on the (*Z*)-thiosilylketene acetal as well as the bulky thioester group (SR) and the ligand architecture. This transition state model may explain the higher selectivities observed for the (*Z*)-thiosilylketene acetals as their isomeric counterparts would suffer from destabilizing interactions upon attack from either enantioface of the (*E*)-thiosilylketene acetal. In addition, this analysis may explain the increase in the diastereoselectivity observed with bulkier R^1-substituents on the thiosilylketene acetal (Table 1, entry 3, $R^1 = {}^i$Pr) as this would serve to further disfavor competing transition states.

In summary, the use of the cationic [Sc-pybox]$(Cl)_2^+$ complexes as chiral Lewis acids for the glyoxylate aldol process with both silylketene acetals and aryl enolsilanes has been accomplished. This study has clearly demonstrated that the choice of counterion can be an important design element in the development of an enantioselective catalytic reaction. The enantioselective aldol processes described provide rapid access to a broad range of malate and α-hydroxy-γ-ketoester synthons that are not readily available from natural sources. The malate products from the glyoxylate aldol reaction are orthogonally protected diesters that can be differentially functionalized, a feature of considerable synthetic value. Both the malate and α-hydroxy-γ-ketoester products obtained from this methodology are useful chiral synthons for the preparation of medicinal agents.[12] Further studies aimed at expanding the synthetic utility of these pybox-scandium catalysts are in progress.

Acknowledgment. Support has been provided by the National Science Foundation and the National Institutes of Health (GM3328-18). A predoctoral NDSEG Fellowship from the ASEE (J.W.) is gratefully acknowledged.

Supporting Information Available: General experimental procedures and full characterization of compounds **3a**−**f** and **5a**−**f**, crystallographic data for compound **5e**, and stereochemical proofs. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The application of this methodology to the asymmetric synthesis of pantolactone derivatives is described in the following paper in this issue.