## Catalytic, Enantioselective Aldol Additions with Methyl and Ethyl Acetate O-Silyl Enolates: A Chiral Tridentate Chelate as a Ligand for Titanium(IV)

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Asymmetric catalysis of the Mukaiyama aldol reaction has been reported with complexes derived from Al, B, Sn(II), and Ti(IV).<sup>1</sup> The levels of asymmetric induction for the addition of propionate-, isobutyrate-, and acetate-derived silyl thioketene acetals to aldehydes parallel those obtained with chiral-auxiliarybased methodologies.<sup>2</sup> However, silyl ketene acetals derived from *O*-alkyl acetates uniformly provide aldolates possessing lower levels of asymmetric induction. We have initiated a study aimed at the design and synthesis of chiral Ti(IV) complexes that catalyze the enantioselective Mukaiyama aldol of *O*-trimethylsilyl, *O*methyl, and *O*-ethyl ketene acetals with aldehydes. We report herein a catalyst that consists of a tridentate ligand derived from 3, Ti(O'Pr)<sub>4</sub>, and 3,5-di-*tert*-butylsalicylic acid.<sup>3</sup> This catalyst (2–5 mol %) furnishes aldol adducts in good yields and high levels of asymmetric induction (88–97% ee).

The design of ligands for catalysts for the Mukaiyama aldol addition have primarily included bidentate chelates derived from optically active diols,<sup>1a,k</sup> diamines,<sup>1bj</sup> amino acids,<sup>1c-e,h,i</sup> and tartrates.<sup>1f,g</sup> Enantioselective reaction processes utilizing chiral Ti(IV) complexes have proven to be some of the most powerful transformations available to the synthetic chemist.<sup>4</sup> However, the propensity of Ti(IV) complexes to form multinuclear aggregates results in complex dynamic equilibria that can render mechanistic and structural analysis difficult.

We have investigated complexes prepared from  $Ti(O'Pr)_4$  and tridentate ligands derived from 2-amino-2'-hydroxy-1,1'-binaphthyl (1) (Scheme 1). This amino alcohol serves as a useful scaffold for the construction of multidentate ligands for Ti(IV) and possesses several salient features: (1) facile synthesis; (2) easy derivatization of the amine; and, consequently, (3) amenability to incremental variations in the overall electronics and sterics of the metal-ligand complex.<sup>5</sup> In addition, we anticipated that tridentate ligands derived from 1 would generate well-defined

(2) (a) Evans, D. A. Aldrichimica Acta 1982, 15, 23. (b) Heathcock, C. H. In The Aldol Addition Reaction; Morrison, J. D., Ed.; Asymmetric Synthesis; Academic Press: San Diego, CA, 1984; Vol. 3, Chapter 2.

(3) Oguni and co-workers have described chiral Schiff base titanium alkoxide complexes which catalyze the enantioselective (62-97% ee) addition of TMSCN to aldehydes; see: Hayashi, M.; Miyamoto, Y.; Inoue, T.; Oguni, N. J. Org. Chem. 1993, 58, 1515. See also: Nitta, H.; Yu, D.; Kudo, M.; Mori, A.; Inoue, S. J. Am. Chem. Soc. 1992, 114, 7969.
(4) (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune,

(4) (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. J. Am. Chem. Soc. 1987, 109, 5765. (b) Duthaler, R. O.; Hafner, A. Chem. Rev. 1992, 92, 807.

(5) For a discussion of electronic tuning in asymmetric catalysis, see: Jacobsen, E. N.; Zhang, W.; Guler, M. L. J. Am. Chem. Soc. 1991, 113, 6703.





Scheme 2



mononuclear Ti(IV) complexes that would be amenable to structural and mechanistic studies.<sup>6</sup>

Amino alcohol 1 was prepared in a single step in 46% ee following the procedure described by Smrcina and Kocovsky (Scheme 1).<sup>7</sup> Two successive fractional recrystallizations from benzene provide 1 in >99% ee. Condensation of 1 with 3-bromo-5-tert-butylsalicylaldehyde (2) affords Schiff base 3 as a crystalline solid.<sup>8,9</sup> Treatment of 3 with Ti(O'Pr)<sub>4</sub> in toluene (23 °C) and subsequent evaporation of the solvent *in vacuo* affords 4 as an orange solid.<sup>10,11</sup>

A solution of benzaldehyde, O-trimethylsilyl O-ethyl ketene acetal (5a),<sup>12</sup> and 5 mol % 4 at 0 °C (4 h) afforded a mixture of aldol products 7 and 8 in 12% and 68% yields, respectively (Scheme 2). Conversion of 7 to the corresponding Mosher (S)-MTPA ester and analysis by <sup>1</sup>H NMR spectroscopy revealed that 7 had been formed in 78% ee.<sup>13</sup> A similar analysis of the (S)-MTPA ester derived from 8 revealed that it had been formed in 64% ee. We interpret the isolation of carbinol 7 (12%) to be consistent with a mechanism that proceeds via intermediate 6. For such a mechanism, following the formation of 6, the Me<sub>3</sub>Si moiety is transferred to either the isopropoxide or the aldolate nonspecifically.

We then proceeded to investigate the effect of exchanging the isopropoxide counterions with less basic oxyanions. We speculated that a salicylate ligand might produce Ti(IV) complexes with

(6) For elegant studies on the mechanism of the asymmetric epoxidation, see: Finn, M. G.; Sharpless, K. B. J. Am. Chem. Soc. 1991, 113, 113.

(7) Smrcina, M.; Polakova, J.; Vyskocil, S.; Kocovsky, P. J. Org. Chem. 1993, 58, 4534.

(8) Jacobsen has described the preparation of a large range of substituted salicylaldehydes; see: Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. J. Org. Chem. 1994, 59, 1939.

(9) In preliminary investigations, the catalyst prepared with 2 gave yields and enantioselectivities superior to those prepared with the tridentate ligands derived from salicylaldehyde and 5-tert-butylsalicylaldehyde.

(10) Evaporation of toluene *in vacuo* has been reported to effect the removal of the *i*-PrOH liberated upon complex formation of Ti(O'Pr), with bidentate ligands such as  $\alpha, \alpha, \alpha', \alpha'$ -tetraaryl-1,3-dioxolane-4,5-dimethanols; see: Seebach, D.; Plattner, D. A.; Beck, A. K.; Wang, Y. M.; Hunziker, D.; Petter, W. Helv. Chim. Acta **1992**, 75, 2171 and references therein.

(11) The structure of the active catalyst has not yet been determined. The illustrated structures of the Ti(IV) complexes are intended to indicate the putative catalyst composition.

(12) Kita, Y.; Segawa, J.; Haruta, J.; Yasuda, H.; Tamura, Y. J. Chem. Soc., Perkin Trans. 1 1982, 1099.

(13) Dale, J. A.; Dull, D. L.; Mosher, H. S. J. Org. Chem. 1969, 34, 2543.

<sup>(1) (</sup>a) Mikami, K.; Matsukawa, S. J. Am. Chem. Soc. 1994, 116, 4077. (b) Kobayashi, S.; Uchiro, H.; Shiina, I.; Mukaiyama, T. Tetrahedron 1993, 49, 1761. (c) Corey, E. J.; Cywin, C. L.; Roper, T. D. Tetrahedron Lett. 1992, 33, 6907. (d) Parmee, E. R.; Hong, Y.; Tempkin, O.; Masamune, S. Tetrahedron Lett. 1992, 33, 1729. (e) Kiyooka, S.; Kaneko, Y.; Kume, K. Tetrahedron Lett. 1992, 33, 4927. (f) Furuta, K.; Maruyama, T.; Yamamoto, H. J. Am. Chem. Soc. 1991, 113, 1041. (g) Furuta, K.; Maruyama, T.; Yamamoto, H. Synlett 1991, 439. (h) Parmee, E. R.; Tempkin, O.; Masamune, S.; Abiko, A. J. Am. Chem. Soc. 1991, 113, 9365. (i) Kiyooka, S.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. J. Org. Chem. 1991, 56, 2276. (j) Kobayashi, S.; Furuya, M.; Ohtsubo, A.; Mukaiyama, T. Tetrahedron: Asymmetry 1991, 2, 635. (k) Reetz, M. T.; Kyung, S.-H.; Bolm, C.; Zierke, T. Chem. Ind. (London) 1986, 824.

enhanced reactivity. In addition, the salicylate counterion could serve to shuttle the trimethylsilyl moiety between 6 and the silylated aldol product 8 and thereby facilitate regeneration of the catalyst.

The catalyst derived from 3,  $Ti(O'Pr)_4$ , and the commercially available 3,5-di-*tert*-butylsalicylic acid was subsequently examined (eq 1).<sup>14,15</sup> Treatment of 3 with  $Ti(O'Pr)_4$  and 3,5-di-*tert*butylsalicylic acid in toluene at 23 °C followed by solvent removal *in vacuo* affords a yellow solid (9) that is freely soluble in Et<sub>2</sub>O.<sup>16</sup>



When a solution of 5 mol % 9 in Et<sub>2</sub>O at -10 °C is treated with an aldehyde and O-trimethylsilyl, O-ethyl or O-methyl ketene acetal (5a or 5b), silvlated aldol adducts are isolated in excellent yields. For example, the aldol addition reaction of benzaldehyde, O-ethyl O-trimethylsilyl ketene acetal (5a) or O-methyl Otrimethylsilyl ketene acetal (5b), and 2-5 mol % 9 affords the silvlated adduct in 94 and 91% yields, respectively. Analysis of the products was facilitated by treatment of the silvlated aldolates with  $Bu_4NF$  to furnish  $\beta$ -hydroxy esters 10 (Table 1). For each adduct, preparation of the derived (S)-MTPA esters allowed the extent of asymmetric induction to be assayed by <sup>1</sup>H NMR spectroscopy. The absolute configuration of the products was established unambiguously by conversion to the known optically active diols.<sup>1h</sup> For the methyl acetate adducts, the yields and enantioselectivities that we observe exceed or match the best reported values with silvl ketene acetals.1d-g,i In addition, a salient feature of this catalytic system is that the aldol addition reaction is effected with only 2 mol % catalyst. Moreover, slow addition of the substrates to the catalyst solution at low temperature is not necessary.1h,j

The addition of 3,5-di-*tert*-butylsalicylic acid as a counterion has a remarkable effect on the yields, enantioselectivity, and catalytic efficiency in the asymmetric Mukaiyama addition reaction reported herein. In this regard, it is important to note that although the design of metal complexes exhibiting stronger Lewis acidity may lead to an increase in the rate of addition to aldehyde, such catalysts can have the effect of decreasing the

**Table 1.** Catalytic Asymmetric Aldol Additions of Alkyl AceateKetene Acetal

Р' Н +	OSiMe <sub>3</sub>	1. 9 (2 or 5 mol Et <sub>2</sub> O, 4h 2. Bu <sub>4</sub> NF, THF	%); -10 ℃, H	
	5a R = Et 5b R = Me	-	n	10 <sup>°a</sup>
Entry	Aldehyde		ee: R = Et <sup>d</sup>	ee: R = Me <sup>e</sup>
1	Me	сно	92%	97%
2	Me	сно	88%	95%
3	Ph	сно	93%	97%
4	Ph	сно	89%	94%
5	C <sub>6</sub> H <sub>11</sub> CHO		94%	95%
6	PhCHO		93%	96%

<sup>a</sup> Absolute configuration was determined by reduction to the known 1,3-diols.<sup>1h</sup> <sup>b</sup> Yields for two steps (addition and desilylation) range from 72 to 98%. <sup>c</sup> For each entry, the *ee* was determined by preparation of the derived (S)-MTPA ester and analysis by <sup>1</sup>H NMR spectroscopy. <sup>d</sup> 5 mol % catalyst used. <sup>e</sup> 2 mol % catalyst used.

overall rate of product formation by diminishing the rate of aldolate silylation.<sup>17</sup> The salicylate chelate offers a way around this problem. We speculate that the salicylate chelate undergoes silylation in analogy to the (acyloxy)borane moiety in the oxazaborolidene-catalyzed aldol addition reactions.<sup>1h</sup> The metalbound silylated salicylate may subsequently be activated by the octahedral Lewis acidic metal toward intramolecular silyl transfer to the metal aldolate.

The use of a tridentate ligand derived from 3,  $Ti('OPr)_4$ , and 3,5-di-*tert*-butylsalicylic acid affords a chiral Ti(IV) catalyst which has been employed for the enantioselective Mukaiyama aldol addition reaction of ethyl and methyl acetate-derived silyl enolates with aldehydes. The catalyst system is general in its scope, affording excellent levels of enantioinduction for both aliphatic and aromatic aldehydes.

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Supplementary Material Available: Experimental procedures and spectral data for all compounds (10 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

<sup>(14)</sup> Jacobsen has utilized ligands prepared from di-*tert*-butyl-substituted salicylaldehydes in the preparation of enantioselective catalysts for asymmetric epoxidation; see: Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. J. Am. Chem. Soc. **1991**, 113, 7063.

<sup>(15)</sup> The catalyst generated from 3, Ti('OPr)<sub>4</sub>, and salicylic acid gave aldol product in 85% ee, albeit in only 19% yield.

<sup>(16)</sup> Studies on the solution structure of 9 and related tridentate salicylimine catalysts are ongoing and will be reported at a later time.

<sup>(17)</sup> Thus, increasing the strength of the RCHO-Ti interaction inevitably leads to an increase in the strength of the R'O-Ti bond. For strong M-O bonds the rate of silylation of the metal aldolate might be prohibitively slow, allowing a silicon-catalyzed process to compete effectively; see: Carreira, E. M.; Singer, R. A. Tetrahedron Lett. **1994**, 35, 4323.