washed with H_2O (2×) and saturated NaCl (2×), and dried ($MgSO_4$). Concentration of the filtrate provided crude **34** that was used immediately in the next reaction. A sample was purified by flash chromatography (short column of silica gel, 5:1 hexane–ether) for characterization purposes: R_f 0.22 (5:1 hexane–ether); $[\alpha]^{27}_D$ +11° (c = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz) δ 7.25–7.40 (m, 10 H), 6.89 (d, J = 2.4 Hz, 1 H), 6.72 (d, J = 2.4 Hz, 1 H), 6.09 (ddt, J = 17.2, 10.6, 5.4 Hz, 1 H), 5.69 (ddd, J = 8.4, 10.0, 17.4 Hz, 1 H), 5.46 (ddt, J = 17.2, 1.4, 1.4 Hz, 1 H), 5.36 (s, 2 H), 5.32 (ddt, J = 10.6, 1.4, 1.4 Hz, 1 H), 5.21 and 5.22 (AB, J = 6.0 Hz, 2 H), 4.87 (dd, J = 1.4, 10.0 Hz, 1 H), 4.77 (s, 2 H), 4.75 (s, 2 H), 4.75 (dd, J = 1.4, 17.4 Hz, 1 H), 4.60 (ddd, J = 1.2, 1.2, 5.4 Hz, 2 H), 4.15 (dq, J = 6.0, 6.8 Hz, 1 H), 3.93 (dd, J = 5.6, 6.0 Hz, 1 H), 3.90 (s, 3 H), 3.72 (dd, J = 5.2, 6.8 Hz, 1 H), 3.50 (s, 3 H), 3.20 (apparent d, J = 10.4 Hz, 1 H), 3.15 (dd, J = 5.2, 6.0 Hz, 1 H), 2.63–2.70 (m, 2 H), 1.5–1.65 (m, 8 H), 1.3–1.4 (m, 2 H), 1.33 (d, J = 6.0 Hz, 3 H), 0.92 (s, 9 H), 0.13 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (75.4 MHz) δ 168.8, 157.6, 154.7, 150.2, 139.3, 138.0, 137.8, 137.1, 136.2, 132.9, 128.6, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 125.8, 125.1, 117.9, 116.4, 114.2, 108.6, 103.9, 101.5, 99.6, 93.7, 91.4, 85.3, 82.4, 73.4, 71.6, 70.5, 69.9, 68.8, 63.9, 61.1, 52.1, 46.9, 36.9, 33.3, 26.4, 26.2, 25.5, 23.9, 20.5, 18.3, -3.6, -3.8; IR (CH_2Cl_2) 1725, 1620 cm^{-1}; HRMS, calcd for $C_{53}H_{70}O_{11}Si$ 910.4689, found 910.4671. Anal. Calcd for $C_{53}H_{70}O_{11}Si$: C, 69.86; H, 7.74. Found: C, 69.98; H, 7.48.

Methyl 8,9-Bis[(benzyloxy)methoxy]-1-hydroxy-3-[(2′*R*,3′*S*,4′*R*,5′*S*,6′*R*)-3′-methoxy-5′,6′-(cyclohexylidenedioxy)-4′-[(*tert*-butyldimethylsilyl)oxy]-2′-vinylheptyl]naphthoate (35). Bu_3SnH (20 μL, 0.074 mmol) was added dropwise to a solution of the crude naphthoate **34** (prepared in the previous experiment; theoretically 0.062 mmol), $Pd(PPh_3)_4$ (1.4 mg, 0.001 mmol), and AcOH (3.7 μL, 0.065 mmol) in toluene (0.3 mL) at 23 °C under N_2. Ten minutes later the reaction mixture was diluted with saturated aqueous NH_4Cl, extracted with CH_2Cl_2 (3×), filtered through a cotton plug, and concentrated to a yellow oil (121 mg). Purification of this material by flash chromatography (silica gel, 5:1 hexane–EtOAc) gave 50 mg (92% from naphthol **33**) of **35** that turned yellow on standing: R_f 0.20 (5:1 hexane–EtOAc); $[\alpha]^{27}_D$ +13° (c = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz) δ 7.25–7.40 (m, 10 H), 7.10 (s, 1 H), 6.83 (d, J = 2.4 Hz, 1 H), 6.66 (d, J = 2.4 Hz, 1 H), 5.65 (ddd, J = 8.4, 10.0, 17.2 Hz, 1 H), 5.59 (s, br, 1 H), 5.34 (s, 2 H), 5.20 and 5.19 (AB, J = 5.6 Hz, 2 H), 4.83 (dd, J = 1.6, 10.0 Hz, 1 H), 4.76 (s, 2 H), 4.72 (s, 2 H), 4.72 (dd, J = 1.6, 17.2 Hz, 1 H), 4.16 (dq, J = 6.0, 6.8 Hz, 1 H), 3.94 (dd, J = J = 5.6 Hz, 1 H), 3.90 (s, 3 H), 3.75 (dd, J = 5.6, 6.8 Hz, 1 H), 3.51 (s, 3 H), 3.18–3.21 (m, 1 H), 2.16 (dd, J = J = 5.6 Hz, 1 H), 2.60–2.71 (m, 2 H), 1.5–1.7 (m, 8 H), 1.3–1.4 (m, 2 H), 1.34 (d, J = 6.0 Hz, 1 H), 0.92 (s, 9 H), 0.13 (s, 3 H), 0.10 (s, 3 H); ^{13}C NMR (100.6 MHz) δ 169.0, 155.0, 154.9, 150.3, 138.9, 138.0, 137.7, 137.0, 136.1, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 125.4, 124.7, 116.6, 113.6, 108.8, 103.9, 103.2, 99.5, 93.6, 85.3, 82.2, 77.2, 73.5, 73.3, 71.5, 70.4, 61.1, 52.2, 47.0, 36.9, 36.8, 33.4, 26.2, 25.2, 23.9, 20.5, 18.2, -3.6, -3.8; IR (CH_2Cl_2) 3580, 3500–3100 (br), 1720, 1620 cm^{-1}; HRMS, calcd for $C_{50}H_{66}O_{11}Si$ 870.4376, found 870.4343. Anal. Calcd for $C_{50}H_{66}O_{11}Si$: C, 68.93; H, 7.64. Found: C, 68.57; H, 7.88.

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Supplementary Material Available: ^{1}H NMR spectra for **22**, **29**, and **31** (3 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.

On the Nature of the Katsuki–Sharpless Asymmetric Epoxidation Catalyst

Pierre G. Potvin* and Stephen Bianchet

Department of Chemistry, York University, 4700 Keele Street, North York, Ontario, Canada M3J 1P3

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The ternary complexes formed by reactions of $Ti_2DIPT_2(O^iPr)_4$ (H_2DIPT = (2*R*,3*R*)-diisopropyl tartrate) with *N*-benzoyl-*N*-phenylhydroxylamine, triethylamine, and diisopropylamine (**3–5**) were examined by NMR spectroscopy in order to link solid-state with solution-state structures and to obtain NMR data for chelating DIPT units lacking ester coordination. The chemical shift differences and the coupling constants between the tartrate skeletal methines in these three complexes were significantly different from those in tartrate complexes previously examined. A linear relation was found between the chemical shift differences at methine positions in various tartrate ester–Ti(IV) alkoxide complexes (i.e. Katsuki–Sharpless catalysts), and the coupling constants ($^3J_{HH}$) between them. The H–C–C–H dihedral angles among the 2:2 complexes were calculated to span about 30°. Parallel changes in the ^{13}C-NMR positions and in the $^1J_{HC}$ and $^2J_{HC}$ values indicated that as the $^3J_{HH}$ values increase, the methines become more and more similar. Further, shielding of one OC*H* by metal-bound carbonyl was deduced to be at the origin of the ^{1}H-NMR chemical shift changes accompanying the angle changes. Along with supporting IR, kinetic, and other evidence, it is argued that these trends reflect a transition between chelating and nonchelating modes of diolate ligation, the latter being stabilized by stronger carbonyl coordination and π donation, and served to confirm that the parent catalyst, $Ti_2DIPT_2(O^iPr)_4$, is best represented by an open, monocyclic structure (A). The pentacoordination implied in A can explain much of the reactivity of $Ti_2DIPT_2(O^iPr)_4$ compared to that of the hexacoordinate complexes of non-tartrate diols. It is argued that the various ester–alkoxide combinations will equilibrate and catalyze epoxidations by the same mechanisms and via the same open structure. Explanations are provided for the success in epoxidation with tartrates, for the lack of success with non-tartrates, and for the epoxidation behavior with two tartrate homologues.

Introduction

The Katsuki–Sharpless (K–S) asymmetric epoxidation (AE) of allylic alcohols by ^{t}BuOOH and the related kinetic resolution of 1(*R*)-substituted allylic alcohols are rare examples of general, catalytic chiral induction processes with predictable outcomes.[1] The major catalytic species in both cases has the formula $Ti_2DIPT_2(O^iPr)_4$[2] (H_2DIPT = (*R*,*R*)-diisopropyl tartrate), but its study is complicated by its fluxional nature and its high reactivity. Early on,[2] $Ti_2DIPT_2(O^iPr)_4$ was assigned structure A in accord with the available NMR and IR evidence and in analogy with the crystal structures of tartrate salts of transition metals.[3]

(1) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(2) Sharpless, K. B.; Woodard, S. S.; Finn, M. G. *Pure Appl. Chem.* **1983**, *55*, 1823.

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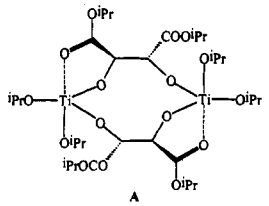
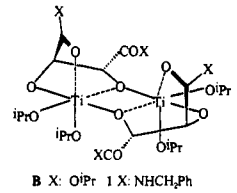
A mechanism based on A was drawn[2] to satisfactorily account for the remarkable enantioselectivity that it shows. Comparative ^{1}H- and ^{13}C-NMR spectra of a number of complexes of chiral 1,2-diols supported that assignment.[4,5] Recently, however, $Ti_2DIPT_2(O^iPr)_4$ has been assigned structure B in analogy with the crystal structure of the related complex **1**[6] with support from new ^{17}O-NMR data obtained with labeled material[7] and the mechanism was appropriately modified to use B as the template.[6,8]



A



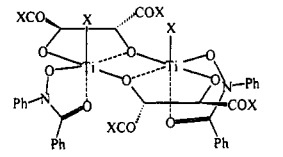
B X: OiPr 1 X: NHCH2Ph

As discussed below, there are several problems with both the new structure assigned to the K–S catalyst and the modified mechanism of AE, especially with respect to the body of NMR data[4,5] but also with respect to certain other bits of information concerning this and other diol complexes, including the C=O band assignments in the IR spectra, the thermodynamics of intramolecular equilibration, the kinetics of epoxidation, and the enantioselectivities in AE. The clarification of these problems is critical to the understanding of the workings of this catalyst, especially in view of its unique selectivity, and to the design of new chiral Lewis acid templates. Unfortunately, there is no convenient spectroscopic handle on the coordination number or geometry of Ti^{IV} alkoxides in solution and such information must be inferred from less direct sources. As discussed below, the ^{17}O-NMR results were not conclusive and can be differently interpreted. Further, crystal structures are at times misleading. For instance, the existence of **1** in solution could not be confirmed[4] nor could the solid-state structure of the 2:3:2 $Ti(O^iPr)_4$:H_2DIPT:HONPhBz complex[6] be reproduced in solution.[9] Moreover, Erker et al.[10] have recently reported a Zr–tartrate complex that adopts one structure in solution and another in the crystal.

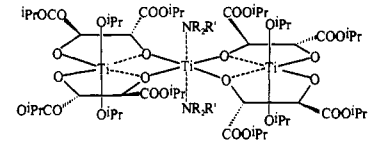
In this paper, we uncover some very informative trends in the ^{1}H- and ^{13}C-NMR spectra of several binary and ternary tartrate complexes and bring together the accumulated evidence from all other sources to infer the structure and mode of action of the K–S catalyst.

Results

The ternary complex $Ti_2DET_2(ONPhBz)_2(OEt)_2$ (**2**) (H_2DET = diethyl tartrate) has been crystallized and found to possess chelating DET units lacking ester carbonyl coordination.[6] In order to obtain NMR data for a DIPT unit in the same binding mode and in order to provide a link between solid and solution states, the isopropoxy analogue $Ti_2DIPT_2(ONPhBz)_2(O^iPr)_2$ (**3**) was prepared and examined in solution. Complex **3** could not be isolated in the same manner as was **2**, as it failed to crystallize, but adding 1 equiv of *N*-benzoyl-*N*-phenylhydroxylamine (HONPhBz) to $Ti_2DIPT_2(O^iPr)_4$ in $CDCl_3$ at room temperature produced a mixture whose spectra were dominated by signals entirely consistent with **3** (free H_2DIPT and $Ti(ONPhBz)_2(O^iPr)_2$ were also present as side products). In accord with structure **3**, there was no sign in the NMR spectra of ester carbonyl coordination (pairs of *C*=O and ester O*C*H peaks were found at positions near those of H_2DIPT compared to strong downfield shifts observed for coordinated ester signals with $Ti_2DIPT_2(O^iPr)_4$ or $Ti_2DIPT(O^iPr)_6$[4,7]) and any intra-tartrate exchange was very slow as the skeletal O*CH* signals appeared as an AB system ($\Delta\delta^{OCH}$ = 0.20 ppm) with large $^3J_{HH}$ (9.05 Hz). This was matched with a large spread between the tartrate's skeletal OCH peaks in the ^{13}C-NMR spectrum ($\Delta\delta^{OCH}$ = 4.21 ppm). Analogous results have been obtained with 8-hydroxyquinoline.[9]



2 X: OEt 3 X: OiPr



4 R = R' = Et
5 R = iPr R' = H

Very similar AB systems also appeared when $Ti_2DIPT_2(O^iPr)_4$ was treated in solution with simple amines such as NEt_3 and NH^iPr_2, but the reactions did not proceed to completion. By signal integration and careful titration experiments, the new products were deduced to be 3:4:2 Ti–DIPT–amine adducts that engage in rapid equilibria with free amine, free H_2DIPT, and $Ti_2DIPT_2(O^iPr)_4$, and which defied all attempts at isolation. The NMR spectra revealed single types of amine, TiO^iPr, and DIPT units. There was no sign of ester coordination nor of intra-tartrate equlibration as the tartrates gave rise to single AB systems with $\Delta\delta^{OCH}$ = 0.18–0.20 ppm and $^3J_{HH}$ = 9.1–9.4 Hz resembling that in **3**. More modest $\Delta\delta^{OCH}$ values were noted, but the data were consistent with structures **4** and **5**. Six other examples of such adducts from both H_2DIPT and H_2DET have been characterized.[9]

These new products were all more stable than $Ti_2DIPT_2(O^iPr)_4$ toward hydrolysis by atmospheric moisture.

Finally, in order to enable comparisons with $Ti_2DIPT_2(O^iPr)_4$, $Ti_2DIPT(O^iPr)_6$, and the ternary species, the ^{1}H-coupled and -decoupled ^{13}C-NMR spectra of the previously described[7] K–S variants $Ti_2DIPT_2(O^tBu)_4$, $Ti_2DET_2(O^tBu)_4$, and $Ti_2DMT_2(O^tBu)_4$ (H_2DMT = (*R*,*R*)-dimethyl tartrate) were obtained in $CDCl_3$ at −20 °C, at which temperature the intramolecular equilibrations were all slow. The ^{1}H-NMR spectra were as reported,[7] with larger $\Delta\delta^{OCH}$ and smaller $^3J_{HH}$ values than had been measured with $Ti_2DIPT_2(O^iPr)_4$. The ^{13}C-NMR spectra also showed paired peaks, indicative of asymmetric tartrate ligation, and the differences between the pairs reached larger values than was generally found with **3**–**5**. Interestingly, the larger the $^3J_{HH}$ value, the smaller the $\Delta\delta^{OCH}$ and $\Delta\delta^{OCH}$ values. In contrast with the ternary species, $Ti_2DET_2(O^tBu)_4$ and $Ti_2DMT_2(O^tBu)_4$ also showed downfield-shifted ester *C*=O and OCH peaks, indicative of ester carbonyl coordination. In the case of $Ti_2DIPT_2(O^tBu)_4$, only one *C*=O peak was detected. As well, the downfield ester OCH signal was broader than the upfield partner. The same was true for the downfield skeletal OCH and the upfield skeletal O*CH* peak. We surmise that the missing *C*=O peak was simply too broad to detect.

(3) Tapscott, R. E.; Belford, R. L.; Paul, I. C. *Coord. Chem. Rev.* **1969**, *4*, 323. Robbins, G. L.; Tapscott, R. E. *Inorg. Chem.* **1976**, *15*, 154.
(4) Potvin, P. G.; Gau, R.; Kwong, P. C. C.; Bianchet, S. *Can. J. Chem.* **1989**, *67*, 1523.
(5) Bianchet, S.; Potvin, P. G. *Can. J. Chem.* **1991**, in press.
(6) Williams, I. D.; Pedersen, S. F.; Sharpless, K. B.; Lippard, S. J. *J. Am. Chem. Soc.* **1984**, *106*, 6430.
(7) Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1990**, *113*, 113.
(8) (a) Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 8. (b) Johnson, R. A.; Sharpless, K. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 7, Chapter 3.2.
(9) Potvin, P. G. Manuscript in preparation.
(10) Erker, G.; Dehnicke, S.; Rump, M.; Krüger, C.; Werner, S.; Nolte, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1349.

Table I. Coupling Constants ($^3J_{HH}$, in Hz), Downfield Displacements from Free Ligand Positions (in ppm) of Upfield ($\delta_u-\delta_f$) and Downfield ($\delta_d-\delta_f$) OC*H* Signals, and Spreads (in ppm) between Skeletal OC*H* ($\Delta\delta^{OCH}$), Skeletal O*CH* ($\Delta\delta^{OCH}$), Ester *CO* ($\Delta\delta^{CO}$), and Ester OCH_n ($\Delta\delta^{ester}$) Signals

complex	$^3J_{HH}$	$\delta_d-\delta_f$	$\delta_u-\delta_f$	$\Delta\delta^{OCH}$	$\Delta\delta^{OCH}$	$\Delta\delta^{CO}$	$\Delta\delta^{ester}$
$Ti_2DIPT(O^iPr)_6$[a]	0	0.71	0.27	0.44	3.43	6.77	3.24
$Ti_2DMT_2(O^tBu)_4$	1.8[b]	0.67[b]	0.33[b]	0.34[b]	3.96[c]	2.98[c]	0.53[c]
$Ti_2DET_2(O^tBu)_4$	3.0[b]	0.65[b]	0.39[b]	0.26[b]	3.69[c]	3.40[c]	0.73[c]
$Ti_2DIPT_2(O^tBu)_4$	4.7[b]	0.67[b]	0.51[b]	0.16[b]	2.19[c]	[d]	0.28[c]
$Ti_2DIPT_2(O^iPr)_4$[a]	7.0	0.67	0.65	0.03	0.20	≈5	2.29
$Ti_2DIPT_2(ONPhBz)_2(O^iPr)_2$ (3)[c]	9.05	0.85	0.65	0.20	4.21	0.49	0.46
$Ti_3DIPT_4(NH^iPr_2)_2(O^iPr)_4$ (5)[c]	9.07	0.86	0.66	0.20	0.74	0.34	0.39
$Ti_3DIPT_4(NEt_3)_2(O^iPr)_4$ (4)[c]	9.35	0.87	0.68	0.18	0.58	1.44	0.61
Ti_2(*meso*-DIPT)$(O^iPr)_6$[a]	4.6	0.85	0.67	0.18	2.89	9.60	4.69

[a] Reference 4. [b] Reference 7. [c] This work. [d] Only one peak observed (see text).

Essentially the same spectrum was obtained at −5 °C. Some of the relevant details are gathered in Table I and discussed below.

Discussion

Large $^3J_{HH}$ values of the magnitude measured for the ternary species **3–5** have also been reported for two Cp_2Zr analogues that were also assigned B-like structures in solution and, in one case, in the crystal.[10] Large $^3J_{HH}$ and moderately large $\Delta\delta^{OCH}$ and $\Delta\delta^{OCH}$ values were also found with 2:2:1 Ti:tartrate:amino alcohol complexes, in which one of the two tartrate units was assigned the same binding mode while the other, assigned a nonchelating binding mode, showed somewhat smaller and more variable $^3J_{HH}$ values (7.2–8.6 Hz).[11] This contrasts with the data obtained with $Ti_2DIPT_2(O^iPr)_4$, the 2:1 complex $Ti_2DIPT(O^iPr)_6$, and its meso analogue.[4] At room temperature, $Ti_2DIPT(O^iPr)_6$ is in equilibrium with $Ti_2DIPT_2(O^iPr)_4$ but becomes the dominant species at low temperatures, and it was assigned a chelated B-like structure with ester coordination (**6**).[4] The ^{1}H-NMR spectra showed widely separated tartrate skeletal OC*H* signals ($\Delta\delta^{OCH}$ = 0.44 ppm) with $^3J_{HH} \approx 0$ Hz. (The meso analogue was assigned an analogous structure but it showed a smaller $\Delta\delta^{OCH}$ of 0.18 ppm and, as required by the meso stereochemistry, a different $^3J_{HH}$.) Six other cases of B-like complexes showing relatively large $\Delta\delta^{OCH}$ and small or zero $^3J_{HH}$ values have earlier been identified with non-tartrate diols.[4,5] On the other hand, $Ti_2DIPT_2(O^iPr)_4$ showed singlets at room temperature. When cooled to sufficiently low temperatures to slow the intra-tartrate exchange, a much smaller shift separation (0.03 ppm) but a larger coupling constant (7 Hz) were measured,[4,7] and this had prompted our assignment of nonchelated structure A.[4]

However, Finn and Sharpless have found wider spreads and smaller couplings with analogous complexes obtained from $Ti(O^tBu)_4$ and H_2DIPT, H_2DET, or H_2DMT.[7] Their data, along with data from $Ti_2DIPT_2(O^iPr)_4$, $Ti_2DIPT(O^iPr)_6$, and from **3–5**, are gathered in Table I. Interestingly, one finds a nearly linear correlation between $\Delta\delta^{OCH}$ and $^3J_{HH}$ for the five binary complexes involved[12] (Figure 1, curve a). Further, one finds that $\Delta\delta^{OCH}$ depends mostly on the positions of the upfield signals (Figure 1, curve b) as the downfield partners remain at roughly constant displacements from the free tartrate positions (Figure 1, curve c). These downfield positions are fairly well matched with the upfield positions from **3–5**, and curves b and c can be extrapolated as depicted. While structural assignments based on single chemical shifts are dangerous, chemical shift differences between otherwise similar nuclei can be significant reflections of the environmental differences present and $^3J_{HH}$ values are good indicators of

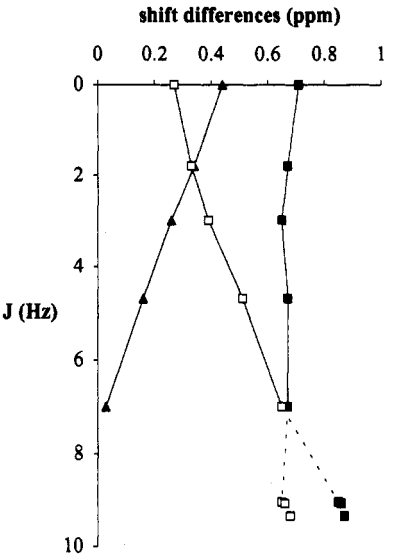


Figure 1. Plots of $^3J_{HH}$ vs chemical shift differences between (a) downfield and upfield ($\Delta\delta^{OCH}$, triangles), (b) upfield and free ligand ($\delta_u-\delta_i$, open squares), and (c) downfield and free ligand ($\delta_d-\delta_f$, filled squares) skeletal OC*H* signals for the species in Table I.

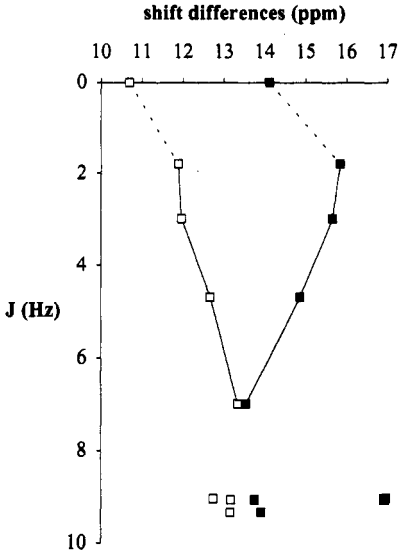


Figure 2. Plots of $^3J_{HH}$ vs chemical shift differences between (a) upfield and free ligand (open squares) and (b) downfield and free ligand (filled squares) skeletal OCH signals for the species in Table I.

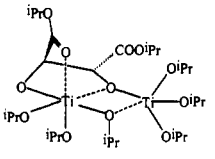
(11) Potvin, P. G. *J. Org. Chem.* **1992**, 3272.

(12) The fifth complex examined by the Sharpless group,[7] $Ti_2DET_2(OEt)_4$, is not included in this analysis as no coupling constant was given. Furthermore, as its secondary alkoxides are prone to form bridges, its structure may be neither A-like nor B-like; indeed, of the five ester–alkoxide combinations examined, it alone equilibrates by an associative, entropy-demanding mechanism.[7]

skeletal conformations. On this basis, this trend indicates a series of conformational states, expressed in $^3J_{HH}$, giving rise to incrementally changing environmental differences expressed in a migrating OC*H* signal (and smoothly changing $\Delta\delta^{OCH}$ values).

In the ^{13}C-NMR spectra, the same sequence of complexes gave rise to an additional trend (Figure 2), though not as linear as in the ^{1}H-NMR data (nor should any linearity be expected in either case) and though $Ti_2DIPT(O^iPr)_6$ was somewhat out of step, perhaps because of the lower temperature used.[4] Nevertheless, the spread in skeletal methine peaks ($\Delta\delta^{OCH}$) also shrank with increasing $^3J_{HH}$. The values of $^1J_{HC}$ and $^2J_{HC}$ for the paired DIPT skeletal OC*H* signals were also informative. For DIPT skeletal methines, the $^1J_{HC}$ values normally span a narrow range near 150 Hz.[9] To a ±0.5-Hz resolution, the $^1J_{HC}$ values with $Ti_2DIPT(O^iPr)_6$ were significantly dissimilar (152.8 and 147.7 Hz), while they were closer in value with $Ti_2DIPT_2(O^tBu)_4$ (151.1 and 153.2 Hz) and virtually identical with $Ti_2DIPT_2(O^iPr)_4$ (152.6 and 153.3 Hz), but only the upfield OCH signal in $Ti_2DIPT_2(O^iPr)_4$ showed a non-zero $^2J_{HC}$ value (2.6 Hz). In contrast, **4** gave $^1J_{HC}$ values of 155.6 and 149.5 Hz matched with $^2J_{HC}$ values of 6.1 and 5.1 Hz, respectively. The significance of the two-bond coupling is not clear, while $^1J_{HC}$ values usually reflect the state of hybridization at C with inductive effects superimposed. These observations echo the ^{1}H-NMR data in suggesting that, among the binary complexes, the initially very different environments of the diolate methines mutate toward ones more similar as the tartrate skeleton twists to give increasing $^3J_{HH}$ values. Hence, if **6** is an accurate description of $Ti_2DIPT(O^iPr)_6$, then $Ti_2DIPT_2(O^iPr)_4$ is better represented by A than by B.

The only pattern to be gleaned from the ester ^{13}C-NMR signals was that the $Ti(O^iPr)_4$-derived binary complexes, including the *meso*-DIPT complex, showed larger spreads than those derived from $Ti(O^tBu)_4$, suggesting that steric hindrance to carbonyl coordination was strong in the latter. However, the C=O band assignments in the IR spectrum[7] (taken at room temperature) definitely imply that $Ti_2DIPT_2(O^iPr)_4$ (1638 cm^{-1}) has stronger carbonyl-to-metal bonds than does $Ti_2DIPT(O^iPr)_6$ (1684 cm^{-1}), though this is not reflected in the ^{13}C-NMR spectra taken at lower temperatures. Stronger carbonyl coordination would be expected in an A-like structure lacking the [2.2.1]bicyclic strain that was found in **1**[6] and that can be expected in any B-like structure such as **6**. Parenthetically, a similar



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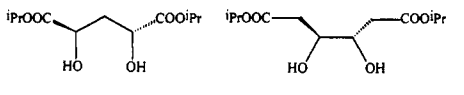


7 8

difference was found with the 2:2 complexes of two tartrate homologues:[13] The *mono*homotartrate 2(*R*),4(*R*)-diisopropyl 2,4-dihydroxyglutarate (**7**) enabled stronger coordination in its complex (1645 cm^{-1}) and was very similar to $Ti_2DIPT_2(O^iPr)_4$ in other respects as well, including the ability to catalyze highly enantioselective AE of primary allylic alcohols. It therefore probably adopts a structure similar to that of $Ti_2DIPT_2(O^iPr)_4$. However, unlike $Ti_2DIPT_2(O^iPr)_4$, it was inefficient in the kinetic resolution of secondary allylic alcohols.[13] This is difficult to explain with a rigid B-like template, but if this kinetic selection depends on a key steric interaction, a poor selectivity could be due to that interaction being weaker or absent in a more flexible A-like structure. The complex of the *bis*homotartrate 3(*R*),4(*R*)-diisopropyl 3,4-dihydroxyadipate (**8**), on the other hand, showed weaker carbonyl coordination (1688 cm^{-1}) than did $Ti_2DIPT_2(O^iPr)_4$ yet its NMR data suited a B-type structure very well.[5,13] Therefore, both cannot be of the B-type since the *bis*homotartrate complex should suffer *less* bicyclic strain, being of a [3.2.1] architecture, and show stronger carbonyl binding than would B itself. Further, it was a poor AE catalyst.[13]

To substantiate the lack of a diolate bridge in $Ti_2DIPT_2(O^iPr)_4$, one could attempt to quantify the amount of skeletal twist involved by estimating the H–C–C–H dihedral angles (θ) from the measured $^3J_{HH}$ values, using as references the crystallographically estimated θ values[14] in **1** (68.4°) and **2** (av 159.7°), but no $^3J_{HH}$ value is available for **1**[4] and no NMR spectra were reported for **2**.[6] Two methods of estimation were used, taking into account a ±0.5-Hz resolution in $^3J_{HH}$. With the simple Karplus[15] relationship $^3J_{HH} = J_{max}\cos^2\theta - 0.28$ Hz, where J_{max} could be estimated at 10.6 Hz using the $^3J_{HH}$ value for **3** and the θ value for **2**, the θ value for $Ti_2DIPT(O^iPr)_6$ is estimated at 90 ± 15.7°. The four binary 2:2 complexes are found to span a range of about 30°, from 114 ± 4° for $Ti_2DMT_2(O^tBu)_4$ to 144.5 ± 2.5° for $Ti_2DIPT_2(O^iPr)_4$ (only values > 90° can be calculated by this relationship). Thus, the change in $^3J_{HH}$ from $Ti_2DIPT(O^iPr)_6$ to $Ti_2DIPT_2(O^iPr)_4$ then represents a change in θ of 36–73°. The best θ–$^3J_{HH}$ correlation for tetrasubstituted ethylenes using group electronegatives, due to Haasnoot et al.,[16] was of limited use as the database used to establish the correlation was primarily composed of substituted cyclohexanes and lacked examples with $^3J_{HH}$ values near 0 or near 7 Hz. Nevertheless, it shows a shallow minimum for $^3J_{HH} = 0$ ± 0.5 Hz at θ = 54–91° for complex **6** but predicts θ = 142° for **3**, some 18° lower than the average crystallographic value for **2**. One can, however, calculate that θ in the four binary 2:2 complexes spans a similar 29° range for θ > 90° (from 100.6 ± 3.4° to 130.0 ± 2.8°) or an even wider range for θ < 90° (from 44.9 ± 3.5° to 11.5 ± 3.8°). By this method, the change in $^3J_{HH}$ from $Ti_2DIPT(O^iPr)_6$ to $Ti_2DIPT_2(O^iPr)_4$ represents a change in θ of at least 39° and up to 83°. Such large differences in θ cannot be accommodated within B-type structures and must signal a change in structure. If the tartrate binding in $Ti_2DIPT(O^iPr)_6$ resembles the tartramide binding in **1**, i.e. with long bonds from the metal to both the carbonyl and bridging diolate oxygens in an unsteady balance (compared to those in **2**[6]), then twisting the tartrate skeleton over such a range must weaken and eventually break the diolate bridge, regardless of the direction of the twist.

Even if the binary complexes were all B-like, their unimolecular equilibration must involve the breaking of diolate bridges, very probably through A-like intermediates or transition states.[7] Thus, the difficulty of equilibration should parallel the strength of the diolate bridges. In accord with this, there is a roughly parallel trend in the $\Delta G^{\ddagger}$ values for the intramolecular positional exchange that

(13) Burns, C. J.; Martin, C. A.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 2826.

(14) From atomic positional parameters (supplementary materials, ref 6). Values of 157.1° and 162.3° were calculated for the two crystallographically distinct tartrate units in **2**.

(15) Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11.

(16) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.

the binary complexes undergo.[7] These were 14.5 kcal mol^{-1} for $Ti_2DIPT_2(O^iPr)_4$, 15.0 kcal mol^{-1} for $Ti_2DIPT_2(O^tBu)_4$ and $Ti_2DET_2(O^tBu)_4$, and 15.4 kcal mol^{-1} for $Ti_2DMT_2(O^tBu)_4$. The equilibration of $Ti_2DIPT(O^iPr)_6$ demands less reorganization and is not, strictly speaking, comparable, but one can estimate $\Delta G^{\ddagger}$ at 13 kcal mol^{-1} from the coalescence of the skeletal OC*H* signals near 0 °C.[4] A similar value (13.3 kcal mol^{-1}) is obtained for the meso analogue.[4] More relevant is the 2:2 complex of the roughly isosteric 1,4-di-*O*-methyl-L-threitol, which was assigned a B-like structure. Here, $\Delta G^{\ddagger}$ can be similarly estimated at 17 kcal mol^{-1} from the coalescence of OCH_3 signals at 57 °C.[4]

Rationale. This interpretation of the NMR data in terms of structural differences must be complemented by palatable explanations of the roles of the ester and monodentate alkoxide groups in inducing structural changes and of the origins of the chemical shift differences. Further, there must be some reasonable explanation why the ester groups of $Ti_2DIPT_2(O^iPr)_4$ do not all coordinate, as is possible in the postulated open, macrocyclic architecture, to generate a fully symmetric, hexacoordinate form rather than A. Finally, the relation of the complex structure to its success in the catalysis of AE can be assessed.

Although the variable and generally larger $\Delta\delta^{OCH}$ and $\Delta\delta^{OCH}$ values achieved with the binary species, in comparison with the ternary species **3–5** lacking ester coordination, do point to an influence from ester coordination, the $\Delta\delta^{CO}$ and $\Delta\delta^{ester}$ values did not increase in step with the decreasing $\Delta\delta^{OCH}$ and $\Delta\delta^{OCH}$ values. Even among the $Ti(O^tBu)_4$-derived complexes, the $\Delta\delta^{CO}$ and $\Delta\delta^{ester}$ values did not seem related to the electron-donating ability of the ester alkyl group. Hence, the carbonyl coordination seems incapable of fully compensating the weakened diolate bridges. However, increasingly strong steric repulsions between the ester groups both within and between tartrate units might be at the origin of the increasing skeletal twist.

On the other hand, a weaker diolate bridge from one tartrate unit could be compensated by π-type donation from both the monodentate alkoxides and the other tartrate's diolate. Such π donation is expressed in shorter Ti–O bonds and more obtuse Ti–O–C angles and has been amply demonstrated, for instance, in $[TiDIPT(O^iPr)Br]_4$[17], in $[Cp_2ZrDMT]_2$[10], and in $[CpTiCl(pinacolate)]_2$.[18] Here, it would occur with terminal, nonchelating diolate oxygens whose attached ester group is not coordinated. In the absence of strong carbonyl coordination in the $Ti(O^tBu)_4$-derived species, π donation from the tartrate will increase with the increasing electron-donating ability of the ester alkyl group and can compensate for the diolate bridges made increasingly long owing to a skeletal twist induced by the increasingly large ester groups. (Logically, this twist would be toward smaller H–C–C–H angles.) In going from $Ti_2DIPT_2(O^tBu)_4$ to $Ti_2DIPT_2(O^iPr)_4$, the O^iPr groups are poorer π donors but the carbonyl coordination is less impeded by steric repulsion with the O^iPr groups. Increasing π donation from the tartrate and stronger carbonyl coordination would lessen the need for a diolate bridge, the ultimate loss of which would eliminate the [2.2.1] bicyclic strain altogether and enable even stronger coordination. Further, π-type donation from the tartrate units precludes the coordination of all ester groups, which would otherwise give hexacoordinate metals and an overall symmetric complex, though the inter-tartrate equilibration

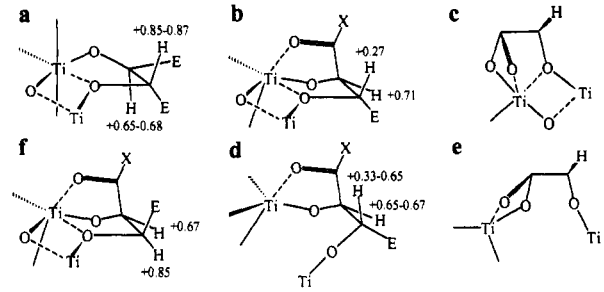


Figure 3. Local structures of tartrate units in various complexes and their chemical shift displacements from free ligand positions, in ppm (X = O^iPr or O^tBu, E = COOMe, COOEt, or COO^iPr).

probably proceeds through such an intermediate. To emphasize its presence, A is therefore drawn with a pair of linear Ti–O–C bond angles. The π donation could in fact explain the recent ^{17}O-NMR results.[7] Complexes of tartrates enriched with ^{17}O at the hydroxyl positions showed two broad bands some 65–150 ppm apart.[19] Given the wide range of observed ^{17}O-NMR chemical shifts (560 ppm), even for simple OH groups (65 ppm), and in view of the lack of signals from authentic bridging alkoxide oxygens (the oligomeric complexes explored showed single resonances[7]), two *O*CH signals 88 ppm apart for $Ti_2DIPT_2(O^iPr)_4$ do not necessarily indicate structure B, as was concluded,[7] but they may well arise from the differently hybridized diolate oxygens in A. Unfortunately, no validation of this hypothesis can be gleaned from the limited data since $\Delta\delta^{OCH}$ values at the slow exchange limits were not available.

Whatever influenced the spread in skeletal methine chemical shifts was evidently not related to the *strength* of ester binding but could instead be a function of the *spatial relation* between the metal-bound ester groups and the neighbouring methines. An explanation for these trends can be advanced in terms of changes in this spatial relation during a transition from B-like to A-like complexation. Firstly, the change from chelation *without* ester coordination in **2–5** (Figure 3a) to that *with* ester coordination in $Ti_2DIPT(O^iPr)_6$ (**6**) (Figure 3b) would orient a metal-bound carbonyl, irrespective of the actual strength of the bond, in an inward-facing position able to shield the bridging OC*H* (Figure 3c) such that its signal (Figure 1, curve b) can shift far upfield while the terminal OC*H* signal would remain relatively unaffected (Figure 1, curve c). Secondly, if the tartrate skeleton in this conformation then twists and the diolate bridge is progressively weakened in going from **6** (Figure 3b) to A (Figure 3d), the metal-bound carbonyl and the skeletal methine would turn progressively away from each other as the metal substituents would rearrange to accommodate a lower coordination number and π-type donation would become more important (Figure 3e); the OC*H* shielding would thus be reduced and the bridging OC*H* signal would migrate downfield. The terminal OC*H* signal (Figure 1, curve c) would again remain relatively unaffected. In support of this scenario, the meso analogue of $Ti_2DIPT(O^iPr)_6$ (Figure 3f) is incapable of suffering that particular shielding effect and it displayed signals very near those of **3–5**. A corollary of this hypothesis is that the bridging OC*H* signals in the binary

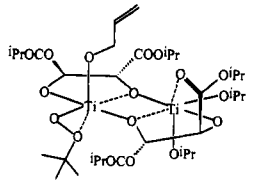
(17) Pedersen, S. F.; Dewan, J. C.; Eckman, R. R.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 1279.

(18) Huffman, J. C.; Moloy, K. G.; Caulton, K. G. *Inorg. Chem.* **1988**, *27*, 2190.

(19) The value of the ^{17}O-NMR data for the species derived from di-L-menthyl (2*R*,3*R*)-tartrate and $Ti(O^iPr)_4$ or $Ti(OEt)_4$[7] cannot be assessed in view of possible transesterifications. Similarly, the data for $Ti_2DIPT(O^tBu)_6$ must be viewed with suspicion since there is no evidence for its existence. In view of the difficulty in forming $Ti_2DIPT(O^iPr)_6$ at room temperature,[4] the 1:2 H_2DIPT–$Ti(O^tBu)_4$ mixture at 318 K is probably very largely dominated by $Ti_2DIPT_2(O^tBu)_4$. Indeed, the data for the 1:2 mixture closely resemble those for $Ti_2DIPT_2(O^tBu)_4$[7].

species are upfield of those of the terminal groups—the same conclusion reached in our recent examination of several complexes of non-tartrate diols with metal-bound side chains[5]—and this is reversed in the meso complex and in the ternary cases lacking the side-chain binding.

These descriptions of the ester complexes apply in the cold, under slow exchange conditions, and in the absence of AE reactants. Since all will suffer extensive exchange of ^{i}PrO or ^{t}BuO groups with primary substrates (and the product epoxy alcohols) during catalytic AE and since ^{t}BuO groups will certainly be exchanged for secondary substrates and products,[20] all of these ester–alkoxide combinations can be considered as functionally very similar and will tend to resemble $Ti_2DIPT_2(O^iPr)_4$. (Though the rates of epoxidation vary in a nonsystematic way with the ester used,[21] a variety of esters have proven useful.[1b]) In the present light, the original A-based mechanism[2] has renewed validity. In comparison with B-like complexes, the lower coordination number depicted in A should greatly enhance the rates of substitution at the metal by enabling an associative mechanism. Indeed, the ternary species **3–5** were noticeably more stable in solution toward hydrolysis by atmospheric H_2O than was $Ti_2DIPT_2(O^iPr)_4$. As well, AE is faster with $Ti_2DIPT_2(O^iPr)_4$ than with $Ti(O^iPr)_4$ or $Ti_2DIPT(O^iPr)_6$.[21] With the former, alcohol–alkoxide exchanges are rapid and the rate-determining step is the oxygen atom transfer,[21] but much slower substrate loading and product unloading steps at hexacoordinate or very bulky centres will become rate-determining. An A-based mechanism also precludes two further difficulties with putative B-like templates: (1) Among the non-tartrate diols that have been explored by NMR, those that form well-defined 2:2 complexes, like **8**, give B-type species, and this has been attributed to their diolate oxygens being more basic than those of tartrate esters and able to provide strong diolate bridges.[4,5] Yet non-tartrate diols, including many not explored by NMR but also of that category, generally do not produce enantioselective AE catalysis.[8a,13] An illustrative case is mannitol diacetonide, affording only 15% ee in AE of (*E*)-α-phenylcinnamyl alcohol[8a] or 28% ee with geraniol.[22] (2) Of the three simplest reactant assemblies for AE with B as the template (C–E), those involving one metal in the oxygen transfer



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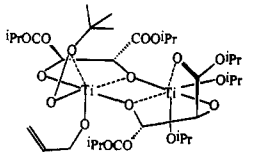

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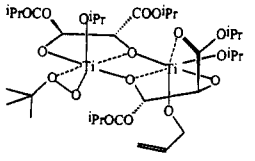

E

step (C[8,23] and D) place the bulky ^{t}BuO group (or the Ph_3CO group of the equally useful trityl hydroperoxide[21]) at axial positions, whereas placing it at the sterically less encumbered equatorial position can be productive if the allylic alcohol is bound to the other metal, as in E—a statistically not improbable event. But, as already discussed,[7] this would not be expected to proceed with much enantiofacial selection since the two competing reaction paths are nearly mirror-symmetric about the axial plane containing the metals. Such a less selective, bimetallic mechanism would be avoided with an A-based assembly but might in fact be operating with the B-like complexes of non-tartrate diols.[24]

Conclusions. Considered together, these lines of evidence point to the presence of a diolate bridge and hexacoordination at one extreme ($Ti_2DIPT(O^iPr)_6$), which confers rigidity and [2.2.1] bicyclic strain, slows the equilibration and gives rise to relatively large $\Delta\delta^{OCH}$ and $\Delta\delta^{OCH}$ values, as opposed to the absence of a diolate bridge and pentacoordination at the other extreme ($Ti_2DIPT_2(O^iPr)_4$), giving rise to minimum $\Delta\delta^{OCH}$ and $\Delta\delta^{OCH}$ values, but enabling stronger carbonyl coordination unimpeded by bicyclic strain, π-type donation from the tartrate diolates and faster equilibration. The pentacoordination would allow fast substitution at the metals and the open architecture would perhaps preclude nonselective epoxidation. In between these extremes, the $Ti(O^tBu)_4$-derived species appear to adopt intermediate structures with weaker carbonyl coordination.

The foregoing suggests that monomeric, pentacoordinate species would constitute desirable candidates for templating AE or other reactions and this is under investigation.

Experimental Section

Methods. For the amine adducts, solutions 37–42 mM in Ti were prepared with due care to exclude moisture by mixing appropriate amounts of solutions of freshly distilled (*R,R*)-diisopropyl tartrate (H_2DIPT) and $Ti(O^iPr)_4$ in $CDCl_3$ (dried over anhydrous $Mg(ClO_4)_2$) into flame-dried NMR tubes. The amines were added neat, by microsyringe, or diluted with $CDCl_3$ to 0.4-mL aliquots, and NMR spectra were obtained at 19–20 °C. No amide formation was detected with $^{i}Pr_2NH$ after 24 h.

For *N*-benzoyl-*N*-phenylhydroxylamine, HONPhBz (Aldrich), 0.4 mL of a 0.16 M stock $CDCl_3$ solution of H_2DIPT was treated with 18 μL of $Ti(O^iPr)_4$ by microsyringe and then with successive 0.5-equiv aliquots of solid HONPhBz. In reverse order, 18 μL of $Ti(O^iPr)_4$ was diluted with $CDCl_3$ and treated with appropriate amounts of solid addend and then with successive 0.2-mL aliquots of the stock solution of H_2DIPT. Spectra were also obtained in the absence of H_2DIPT for comparison.

For the $Ti(O^tBu)_4$-derived complexes, $Ti(O^tBu)_4$ was prepared by repeated treatments of $Ti(O^iPr)_4$ with ^{t}BuOH followed by the removal of volatiles under vacuum and then purified by two distillations. The samples were 0.19 M, prepared by treating 0.3 M $CDCl_3$ solutions of the tartrate esters with 0.524 M $Ti(O^tBu)_4$ in $CDCl_3$, and were examined at 253 K. In the case of H_2DIPT, several hours of aging at 45 °C were allowed for complete reaction. The ^{1}H-NMR spectra at 253 K conformed to the data reported in the literature.[7] ^{1}H-coupled ^{13}C spectra were used to distinguish skeletal OCH from $OCMe_3$ signals in the $Ti(O^tBu)_4$-derived complexes and to measure $^1J_{HC}$ and $^2J_{HC}$ values.

Simultaneous irradiation of the CH_3 region was at times used to simplify the OC*H* regions and to establish the numbers and positions of OC*H* heptets. Single-frequency homo-decoupling (^{1}H–^{1}H) and hetero-decoupling (^{1}H–^{13}C) and 2-dimensional shift correlation experiments were used to establish connectivities.

$Ti_2DIPT_2(ONPhBz)_2(O^iPr)_2$: ^{1}H NMR δ 7.53–7.20 (m, 20 H), 5.22 (AB q, 2 H, J = 9.05 Hz, $\Delta\delta$ = 0.204 ppm, diolate OC*H*), 5.16, 5.04 (2 h, 4 H, ester OC*H*), 4.45 (h, 2 H, TiO^iPr OC*H*), 1.44–0.73 (m, $OCHCH_3$) ppm; ^{13}C NMR δ 171.09, 169.65 (ester

(20) McKee, B. H.; Kalanter, T. H.; Sharpless, K. B. *J. Org. Chem.* 1991, *56*, 6966.
(21) Woodard, S. S.; Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* 1991, *113*, 106.
(22) Kwong, P. C. C.; Potvin, P. G. Unpublished work.
(23) Jorgensen, K. A.; Wheeler, R.; Hoffmann, R. *J. Am. Chem. Soc.* 1987, *109*, 3240.
(24) An alternative explanation for the poor enantioselectivity of non-tartrate diol complexes is that nonselective AE is due to faster catalysis by traces of unreacted $Ti(O^iPr)_4$.[7]

C=O), 164.63 (amide C=O), 140.46, 130.53, 129.37, 128.97, 128.54, 128.07, 128.01, 127.94, 127.85, 125.61, 125.48 (Ph), 88.85, 84.63 (diolate OCH), 79.81 ($TiOCHMe_2$), 68.11, 67.50 (ester OCH), 25.37, 21.64, 21.58 (CH_3) ppm.

$Ti(ONPhBz)_2(O^iPr)_2$: ^1H NMR δ 7.42–7.21 (m, 10 H), 4.99 (h, 2 H), 1.32 (d, 12 H) ppm; ^{13}C NMR δ 163.40 (C=O), 140.94, 130.56, 129.19, 129.02, 128.89, 128.59, 128.17, 128.06, 127.88, 125.66 (Ph), 77.36 (OCH), 25.43 (CH_3) ppm.

$Ti_3DIPT_4(Et_3N)_2(O^iPr)_4$: ^1H NMR δ 5.24 (AB q, 8 H, J = 9.34 Hz, Δδ = 0.184 ppm, diolate OCH), 4.99 (2 h, 8 H, J = 6.32 Hz, ester OCH), 4.83 (h, 4 H, J = 5.91 Hz, $TiOCHCH_3$), 3.28 (b, 12 H, NCH_2), 1.69 (bs, 8 H, OH), 1.30–1.12, 1.07 (m+t, 138 H incl HO^iPr, CH_3) ppm; ^{13}C NMR δ 171.28, 170.79 (C=O), 85.64, 85.06 (diolate OCH), 77.28 ($TiOCHCH_3$), 67.82, 67.36 (ester OCH), 46.18 (NCH_2), 26.00, 25.64, 21.87, 21.70, 21.65 (CH_3) ppm.

$Ti_3DIPT_4(^iPr_2NH)_2(O^iPr)_4$: ^1H NMR δ 5.23 (AB q, 4 H, J = 9.07 Hz, Δδ = 0.196 ppm, diolate OCH), 4.99, 4.98 (2 h, 4 H, ester OCH), 4.83 (h, 2 H, $TiOCHCH_3$), 2.80 (h, NCH), 1.30–1.12 (m, $OCHCH_3$), 1.06 (d, $NCHCH_3$) ppm; ^{13}C NMR δ 171.28, 170.94 (C=O), 85.80, 85.04 (diolate OCH), 77.21 ($TiOCHCH_3$), 68.05, 67.66 (ester OCH), 45.28 (NCH), 26.04, 25.68, 23.23, 21.89, 21.74 (CH_3) ppm.

$Ti_2DMT_2(O^tBu)_4$: ^{13}C NMR δ 174.78, 171.81 (CO), 87.88, 83.92 (skeletal OCH), 86.02, 84.68 ($OCMe_3$), 52.70, 52.17 (OCH_3), 31.26, 31.12 (CCH_3) ppm.

$Ti_2DET_2(O^tBu)_4$: ^{13}C NMR δ 174.85, 171.45 (CO), 87.69, 84.00 (skeletal OCH), 86.08 ($OCMe_3$), 61.85, 61.12 (OCH_2), 31.27, 31.12 (CCH_3), 14.24, 14.03 (CH_2CH_3) ppm.

$Ti_2DIPT_2(O^tBu)_4$: ^{13}C NMR δ 173.28 (CO), 86.65, 84.45 (skeletal OCH), 84.95, 83.14 ($OCMe_3$), 69.24, 68.95 ($OCHMe_2$), 31.95, 31.01 (CCH_3), 22.06, 21.57 ($CHCH_3$) ppm.

Acknowledgment. The author is grateful to Mr. Stephen Balsky for technical assistance and to the Natural Sciences and Engineering Research Council of Canada for financial support.

Notes

The Enzymatic Preparation of (2*R*,3*S*) Phenyl Glycidic Acid Esters

Angelo Gentile and Claudio Giordano

Istituto di Ricerche Chimiche G. Zambon, Via Cimabue 26/28, Cormano, Milano, Italy

Claudio Fuganti, Luca Ghirotto, and Stefano Servi*

Dipartimento di Chimica Politecnico di Milano, Piazza L. da Vinci 32, 20133 Milano, Italy

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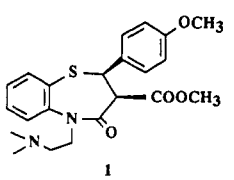
Due to new examples of compounds exhibiting different properties in their enantiomeric forms there is a current growing interest in the preparation of biologically active enantiomerically pure compounds, drugs, and pharmaceuticals. Only a few tenths of the pharmaceuticals on the market are present as single enantiomers, and they mainly arise from fermentation or from classical resolution at some stage of the synthetic sequence; however, their number is expected to grow in the future.[1] Recently, hydrolytic enzymes were successfully used to perform the kinetic resolution of racemates, thus allowing the preparation of enantiomerically pure drugs.[2]

We wish to report a resolution process applied to the synthesis of (2S,3S)-diltiazem 1, an enantiomerically pure drug with calcium antagonist activity.[3] The practical



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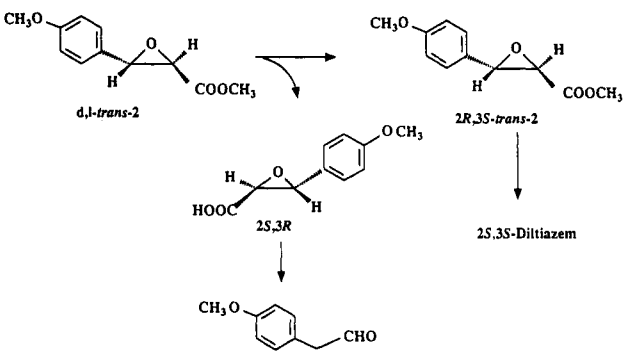

Figure 1.

synthesis of 1 involves the *trans-p*-methoxyphenylglycidic acid (PGA) ester 2 as the first intermediate.[4] Optically active 1 is currently prepared by the classical resolution of an intermediate at a late stage of the synthetic sequence;[5] in practice it would be preferable to carry out the resolution at an early stage of the synthesis so as to avoid processing twice the material necessary in the successive synthesis steps, as is required with a racemic intermediate. This prompted us to investigate the resolution of *rac*-2. Although optically active 2 is currently available through a classical resolution[6] or asymmetric synthesis,[7] we considered an alternative approach: an enzymatic way. As possible enzymatic reagents to perform such a resolution on PGA esters one would first consider the hydrolytic action of lipases because of the unspecificity of such enzymes and, for a more specific fit, α-chymotrypsin (α-CHT), a proteolytic and hydrolytic enzyme which has a preference for phenylpropionic acid derivatives. In fact,

(1) See, for instance: Di Cicco, R. L. *Proceedings of the Chiral 92 Symposium*; Manchester, England, 1992; p 17.
(2) See, for instance: Bertola, M. A.; Desmet, M. J.; Marx, A. F.; Phillips, G. T. Eur. Pat. 0299559-A to Gist-Brocades NV, 1987.
(3) Elks, J.; Ganellin, C. R. *Dictionary of Drugs*; Chapmann and Hall: London, 1990; p 426.
(4) Hashiyama, T.; Inohue, H.; Konda, M.; Takeda, M. *J. Chem. Soc., Perkin Trans. 1* 1984, 1725. Hashiyama, T.; Inoue, H.; Takeda, M.; Aoe, K.; Kotera, K. *J. Chem. Soc., Perkin Trans. 1* 1985, 421.
(5) Senuma, M.; Shibazaki, M.; Nishimoto, S.; Shibata, S.; Okamura, K.; Date, T. *Chem. Pharm. Bull.* 1989, *37*, 3204. Nagao, S.; Kurabayashi, K.; Futamura, N.; Kinoshita, H.; Takahashi, T. Eur. Pat. Appl. 0098892, to Tanabe Seiyaku Co. Ltd., 1984.
(6) Wynberg, H.; Ten Hoeve, W. Eur. Pat. Appl. 0342903A1 to Marion Laboratories, Inc., 1989.
(7) Palmer, J. T. Eur. Pat. Appl. 0342904a2 to Marion Laboratories, Inc., 1989. U.S. Pat. 4.552.695 to Shionogi and Co. Ltd., 1985.

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