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ASYMMETRIC EPOXIDATION MODELS: AN ALKYL HYDROPEROXIDE DEPENDENT CHANGE IN MECHANISM

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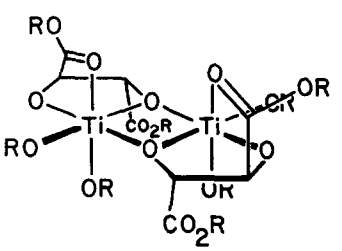
Summary: Titanium(IV)-pyridinediol complex **5** was studied as a model for titanium-tartrate asymmetric epoxidation catalysts. The sign of induction depended on the alkyl group of the alkyl hydroperoxide oxidant. Trityl hydroperoxide gave 64% ee in the direction predicted by the model.

The titanium-tartrate catalyzed asymmetric epoxidation of allylic alcohols[1] has attracted considerable synthetic[2] and mechanistic interest.[3] In the currently held mechanism, the dialkyl tartrate chiral auxiliary and the titanium(IV) isopropoxide precatalyst associate in situ generating a dimeric complex, **1**, which, by the exchange of the remaining monodentate alkoxides for the allylic alcohol and alkyl hydroperoxide, serves as a template for asymmetric epoxidation. Accordingly, transition state **2**, with a meridional arrangement of the allylic alcohol and bidentate alkyl hydroperoxide, spiro orientation of the olefin and peroxide, and wrapping of the allylic alcohol away from the diagonal quadrants blocked by the ester groups, leads to the favored epoxy alcohol enantiomer.



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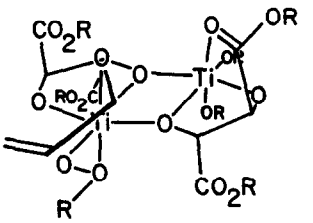

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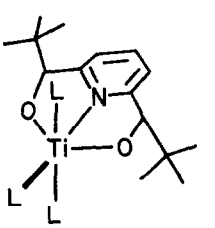

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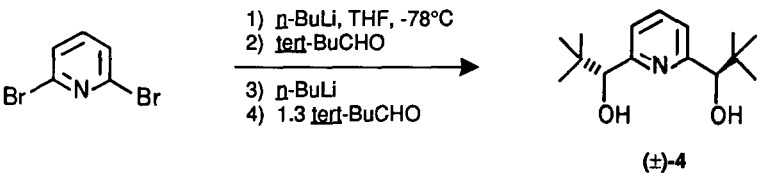
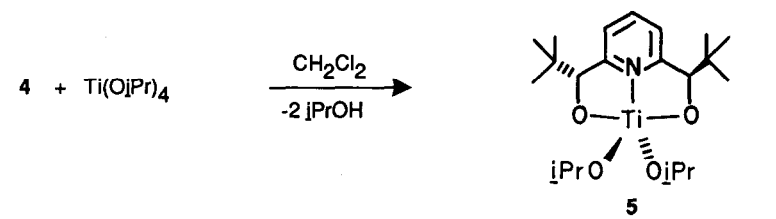
We sought to emulate this scenario with monomeric pyridinediol complexes of type **3**. Complexes **1** and **3** each contain a meridional plane defined by a tridentate ligand. In **1**, this "ligand" contains the two tartrates and the other (equivalent) titanium. This arrangement is analogous to the alkoxide-donor-alkoxide arrangement of **3** if the bridging oxygens in **1** are considered as a donor in the rear and an alkoxide on the right (in reality, they are both intermediate between these

extremes). Furthermore, both ligands sterically congest diagonal quadrants of the titanium's coordination sphere. Thus, if **3** loads its three remaining coordination sites with an allylic alcohol and a bidentate alkyl hydroperoxide and then serves as a template for asymmetric epoxidation with the same meridional-spiro mechanism depicted in transition state **2**, then complex **3** should behave like the titanium-tartrate catalyst.

The requisite pyridinediol ligand **4** was synthesized from 2,6-dibromopyridine in one pot by reiterative lithiation and trapping with pivalaldehyde (35% after chromatography, eq 1), and resolved by multiple recrystallizations of the dibenzoyltartrate salt. Treatment of **4** with one equivalent of titanium(IV) isopropoxide in chloroform-d or dichloromethane gave the symmetric chelate **5** (eq 2),[4] which was found to be monomeric in dichloromethane by the Signor method.[5,6]



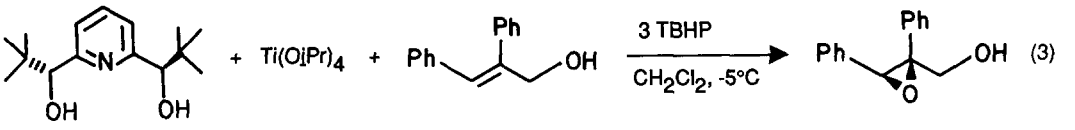
(1)



(2)

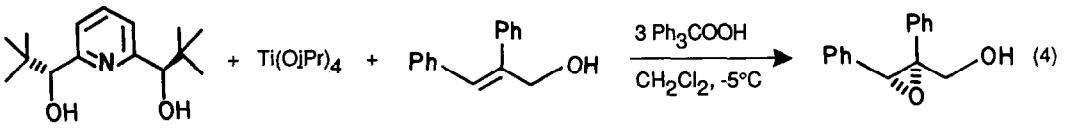
Complex **5** was then tested as a catalyst for asymmetric epoxidation. Exposure of (E)-α-phenylcinnamyl alcohol to a mixture of (R,R)-**4**, titanium(IV) isopropoxide, and tert-butyl hydroperoxide (TBHP) in dichloromethane gave the corresponding epoxide in high yield and 40-41% ee favoring the 2-S enantiomer (eq 3). The enantiomeric excess was found to be independent of the ligand to titanium ratio (x, x=1.25 to 2.00). Setting x at 1.50, but switching to trityl hydroperoxide in place of TBHP, gave the corresponding epoxide in high yield and 52-64% ee, this time favoring the 2-R enantiomer (eq 4). Varying the concentration did not significantly affect the enantioselectivity. The higher value, 64% ee, was obtained at [Ti]=13 mM (the same concentration as for eq 3), and at one fifth this concentration. Increasing the concentration five fold to [Ti]=65 mM produced a cloudy reaction mixture and a small decrease in the ee to 52%.

The consistency of the enantiomeric excess upon variation of the ligand to titanium ratio in equation 3 suggests that (R,R)-**4** is tightly bound such that unbound (achiral) titanium species do not compete. Interestingly, use of two equivalents of (R,R)-**4** did not slow down the reaction significantly, implying that the binding constant for a second equivalent of (R,R)-**4** (which would block sites for epoxidation) is small. Models indicate that this should be the case for the homochiral ligand since the tert-butyl groups would point together in a 2:1 complex. (This situation is in



x equiv

x=1.25 41% ee
x=1.50 40% ee
x=2.00 41% ee



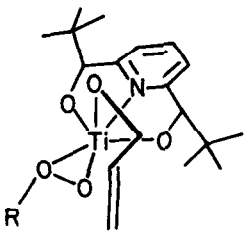
1.5 equiv

[Ti]= 3 mM 64% ee
[Ti]=13 mM 64% ee
[Ti]=65 mM 52% ee

contrast to vanadium(V) catalyzed asymmetric epoxidations with chiral hydroxamate ligands in which sufficient chiral ligand to maximize asymmetric induction stifled the rate of epoxidation.[7]) The monomeric structure of **5** and the consistency of the enantiomeric excess as a function of concentration support the premise of a monomeric catalyst.

The 64% ee obtained above, while small compared to the 98% ee obtained with the titanium-tartrate system with (E)-α-phenylcinnamyl alcohol, is high for a non-tartrate derived chiral auxiliary.[3] The switch in the sense of induction (si vs. re) with the change in alkyl hydroperoxide was unexpected since TBHP and trityl hydroperoxide both give the same selectivity with the titanium-tartrate system.[8] The sense of induction for the 64% ee obtained with trityl hydroperoxide agrees with the above model based on the titanium-tartrate system, while the 41% ee obtained with TBHP disagrees.[9] This switch in face selectivity suggests an alkyl hydroperoxide dependent change in mechanism.

Keeping with the quadrant blocking scenario of transition state **2**, two changes could account for the reversal in face selectivity with the alkyl hydroperoxide in the pyridinediol system: a facial instead of a meridional arrangement of the allylic alcohol and bidentate alkyl hydroperoxide as shown in **6**, or a planar instead of a spiro orientation of the olefin and peroxide as shown in **7**. Of the two situations, a variation between facial and meridional transition states should be more dependent on the alkyl group of the alkyl hydroperoxide. A facial transition state for the titanium-tartrate system was ruled out on steric grounds.[3] A view from above the meridional ligand plane, **8**, shows that there is no room in the shaded area for either the olefin or the alkyl group of the alkyl hydroperoxide, one of which must be placed there in a facial transition state. The same view of the pyridinediol system, **9**, shows that there is more room to accommodate the olefin and the alkyl group of the alkyl hydroperoxide in a facial transition state.[10] If there is sufficient room for a tert-butyl group but not a trityl group, this would account for the reversal in face selection.



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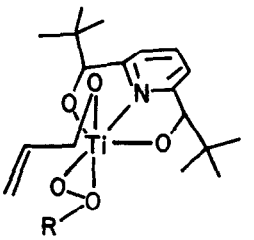

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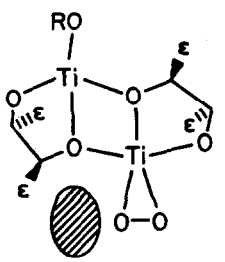

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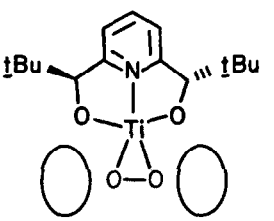

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References and Notes

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