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A Tetradentate Ligand for the Enantioselective Ti(IV)-Promoted Oxidation of Sulfides to Sulfoxides: Origin of Enantioselectivity

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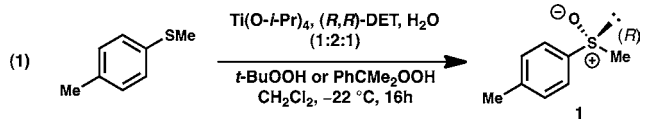
Supporting Information

ABSTRACT: A detailed stereomechanistic analysis has led to the design of a new tetradentate ligand for the enantioselective Ti(IV)-catalyzed oxidation of unsymmetrical sulfides to sulfoxides with high selectivity. The pathway of this oxidation and the closely related and long-known Kagan–Modena oxidation have been clarified to identify the likely origin of the enantioselectivity.

Almost three decades ago, Kagan and co-workers reported that a reagent formed from Ti(O-*i*-Pr)$_4$, (*R*,*R*)-diethyl tartrate (DET), and water in a ratio of 1:2:1 in CH_2Cl_2 catalyzes the reaction of *tert*-butyl hydroperoxide with aryl alkyl sulfides to form the corresponding sulfoxides with enantiomeric excesses (ee's) averaging ca. 80% at −22 °C for prolonged reaction times (eq 1).[1,2] In the absence of water,



considerably lower enantioselectivities were observed. The conditions of catalyst formation and the reaction temperature are absolutely critical. The active catalyst appears to be unstable at higher temperatures, and at lower temperatures both the reaction rate and product ee are markedly diminished.

At about the same time, Modena's group[3] reported similar results using a 4:1 ratio of DET to Ti(O-*i*-Pr)$_4$ and 4 equiv of isopropyl alcohol at −20 °C. Although no water was deliberately added to Modena's reactions, its adventitious presence seems possible. The purpose of the present work was to elucidate both the reaction pathway and the basis for enantioselection in Kagan-type oxidations, which continue to be enigmatic despite much research in this area.[1]

One reason for the difficulty of understanding the basis for enantioselection in the DET–Ti(O-*i*-Pr)$_4$ system emerged from the extensive two-dimensional NMR study of Potvin and Fieldhouse,[4] which revealed the presence of a complex mixture of species, possibly in rapid equilibrium on the reaction time scale. Although the Kagan process is complicated, even more complex modifications of the system have been used for the large-scale synthesis of various pharmaceuticals, most noteworthy of which is the blockbuster product esomeprazole (Nexium).[1]

As detailed in the Supporting Information, extensive and repeated preparative experiments on the Kagan system with purified reagents confirmed that two DETs per Ti(IV) are required for good enantioselectivity and that ca. 1 equiv of H_2O per Ti(IV) is optimal for enantioselectivity, although this can be replaced by isopropyl alcohol (4 equiv per Ti) as in the Modena system.[3]

We also found by a series of preparative experiments that the ee of sulfoxide **1** produced under the optimal Kagan conditions using cumene hydroperoxide (CHP) increased as the time for the oxidation was extended beyond the point at which all of the starting sulfide was consumed. The increase in the ee of the sulfoxide is due to its enantioselective oxidation to the corresponding sulfone. At a reaction time of 16 h, 14 h beyond the disappearance of the starting sulfide, the ee of sulfoxide **1** rose to 96% from ca. 80% at 2 h, accompanied by the formation of methyl *p*-tolylsulfone in 18% yield. In addition, exposure of sulfoxide **1** with 82% ee to Kagan oxidation at −20 °C for 15 h produced sulfoxide **1** with >98% ee plus considerable sulfone.[5] From these results, it is obvious that part of the reason for the success of the reported high enantioselectivity of some Kagan oxidations lies in the use of extended reaction times and the intervention of kinetic resolution of the product **1**.[2f] Previous reports indicate a divergence of views regarding the occurrence of further oxidation to sulfone and whether this influences the ee of the sulfoxide product.[2a,b]

Kagan reported[2a] a nonlinear relationship between the enantioselectivity of sulfoxide formation and the optical purity of DET for the Kagan process. Our own experiments[5] have shown that there is a linear relationship at short reaction times and that the nonlinearity arises at long reaction times, most likely because of further oxidation of the sulfoxide. The linearity shown by our data obviates the requirement to consider an M_2L_4 pathway, as proposed previously.[2d]

We analyzed a number of possible structures for the Kagan process starting from the evidence that two DET ligands are attached via their hydroxyl groups to Ti and the likelihood that the active oxidant also involves η^2-coordinated hydroperoxide. The η^2 mode for coordination of hydroperoxides to titanium(IV),[6] vanadium(V),[7] and even lithium[8] has been documented by X-ray crystallography. In addition, density functional theory (DFT) studies have revealed the favorable nature of η^2 coordination to Ti(IV).[5,9]

There are two possible diastereomers for a hexacoordinate (octahedral or near-octahedral) complex of Ti(IV) with two DETs and one η^2-hydroperoxide ligand.[10] The most stable arrangement of each of these helical isomers was determined by

Received: June 19, 2012
Published: October 9, 2012

dx.doi.org/10.1021/ja305991k | J. Am. Chem. Soc. 2012, 134, 17354–17357

DFT calculations, which indicated the structures shown in Figure 1.[11] The *P* (or Δ) diastereomer (Figure 1A) is more

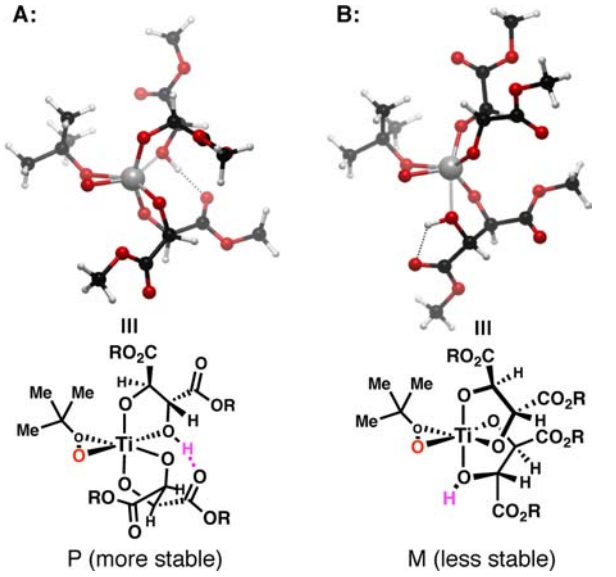


Figure 1. *P* and *M* helical isomers of the complex of Ti(DMT)$_2$ with *t*-BuOOH.

stable than the *M* (or Λ) form (Figure 1B), the calculated energy difference (ΔE_0) being 2.2 kcal/mol.[5,12] To reduce the computational cost, DET was replaced by dimethyl tartrate (DMT) and CHP by *tert*-butyl hydroperoxide.

To locate the lowest-energy structures, several starting geometries were generated by different methods and then optimized by DFT.[11] For all light atoms, this was performed using the B3LYP density functional with the 6-31G* basis set, and for titanium, the Los Alamos National Laboratory electrostatic core potential was used with two double-ζ basis sets (LANL2DZ). Input structures were generated with Spartan '08 using molecular mechanics (Merck molecular force field) and a semiempirical method (Parameterized Model number 3) as well as without optimization.

The B3LYP energy surface of the resulting lowest-energy structure was then explored further by scanning the dihedral angles corresponding to the orientations of the carbomethoxy substituents of the DMT ligands. A proton was then attached to each of the tartrate oxygens on Ti with hydrogen bonding to any nearby electron-donor oxygen. These low-energy structures were finally optimized by moving the one O-bound proton to each of the four other possible locations and then reoptimizing with the proton at each location. The reported electronic energies include a zero-point energy correction and are referenced to the lowest-energy isomer in both cases. To ensure that the minimized structures were true local minima, a standard frequency analysis was performed.[13]

Three-dimensional modeling and stereochemical analysis revealed that the *P* diastereomer of the active oxidant shown in Figure 1 should favor the formation of (*R*)-**1** from methyl *p*-tolylsulfide using Kagan's 2:1 (*R*,*R*)-DET/Ti(O-*i*-Pr)$_4$ catalyst, whereas the corresponding *M* diastereomer is unlikely to lead to enantioselective oxidation. These analyses suggested that DET might advantageously be replaced by a suitable chiral tetradentate ligand that might be superior to a pair of DET subunits for entropic reasons while also favoring the formation of the *P* form of the active oxidant. Tetraol **2** emerged as a potentially superior ligand for the enantioselective Ti(IV)-catalyzed oxidation of sulfides to sulfoxides, not only because it provides the entropic advantage over DET but also because it favors the formation of the *tert*-butylperoxy/COOEt analogue of complex *P*-**3** over the *M* diastereomer by ca. 1.6 kcal/mol, as indicated by DFT calculations (Figure 2).[5,12]

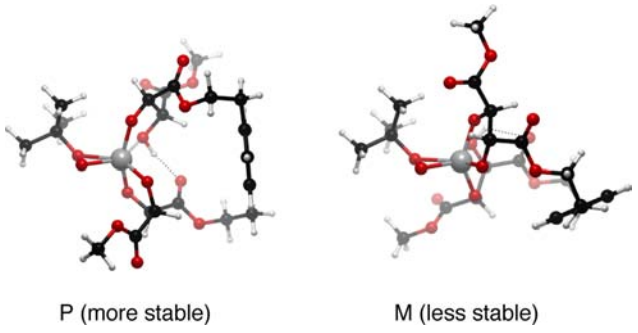


Figure 2. *P* and *M* helical isomers of Ti(**2**) with *t*-BuOOH.

Ligand **2** was conveniently synthesized from the acetonide of (*R*,*R*)-tartaric acid monoethyl ester by the following sequence: (1) conversion to the corresponding acid chloride using (COCl)$_2$ and a catalytic amount of *N*,*N*-dimethylformamide (DMF) in CH_2Cl_2 (initially at 0 °C and then at 23 °C for 12 h); (2) reaction with 1,4-bis(2-hydroxyethyl)benzene and pyridine at 0−23 °C for 24 h; (3) acetonide cleavage using 20 equiv of HF−pyridine and 3 equiv of H_2O at 23 °C for 3 h (Figure 3A).[5]

When methyl *p*-tolylsulfide was oxidized in CH_2Cl_2 at −20 °C with a mixture of ligand **2**, Ti(O-*i*-Pr)$_4$, H_2O (1:1:1 ratio) and 2 equiv of CHP, the starting sulfide was completely consumed in 1 h with the formation of the corresponding sulfoxide (*R*)-**1** (95% conversion by ^{1}H NMR analysis, 90%

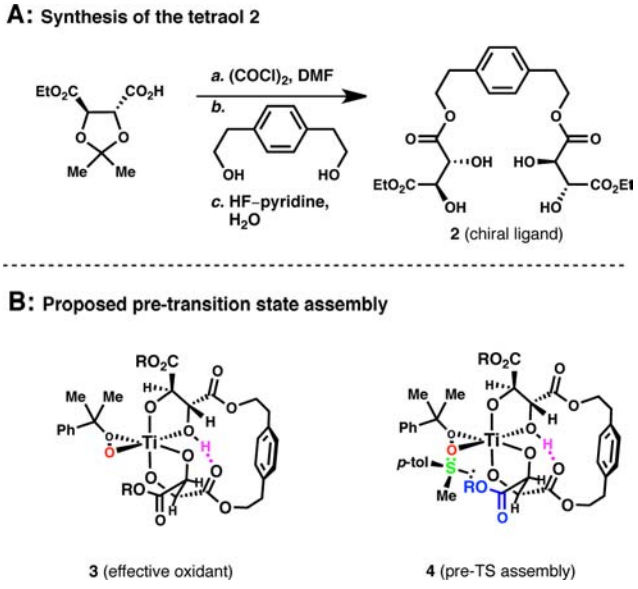


Figure 3. (A) Synthesis of ligand **2**. Reagents and conditions: (*a*) 4.0 equiv of (COCl)$_2$, 0.1 equiv of DMF, CH_2Cl_2 (0.8 M), 0−23 °C, 12 h; (*b*) 0.50 equiv of 1,4-bis(2-hydroxyethyl)benzene, 1.0 equiv of pyridine, CH_2Cl_2 (0.5 M), 0−23 °C, 24 h, 89% (two steps); (*c*) 20 equiv of HF−pyridine, 3.0 equiv of H_2O, CH_3CN (2.8 M), 0−23 °C, 3 h, 77%. (B) Proposed pre-transition state assembly.

dx.doi.org/10.1021/ja305991k | *J. Am. Chem. Soc.* 2012, 134, 17354−17357

isolated yield) with 92% ee (by chiral HPLC analysis), along with a 5% yield of the corresponding sulfone. The absolute configuration of the sulfoxide corresponds to that expected for **3** as the active oxidant, assuming that a sulfide lone pair attacks the coordinated peroxide backside to the O–O bond, with the other lone pair and the methyl and *p*-tolyl groups positioned to minimize steric repulsion (especially with the COOR group of **4**, shown in blue) as shown in the pre-transition state assembly **4** (Figure 3B).

A comparison of the oxidation of sulfides using a combination of **2**, Ti(O-*i*-Pr)$_4$, CHP, and H_2O (1:1:2:1 ratio) with that using the optimum Kagan reagent [2:1:2:1 (*R*,*R*)-DET/Ti(O-*i*-Pr)$_4$/CHP/H_2O] in CH_2Cl_2 at −20 °C is instructive. After a reaction time of 1 h with the Kagan reagent, the conversion of methyl *p*-tolylsulfide to the sulfoxide was only 79% with at best only 80–86% ee. In all cases, the predominating enantiomer is the (*R*)-sulfoxide. The use of 1 equiv of water was beneficial in both cases, since the ee values of the (*R*)-sulfoxide in the absence of water were found to be only 59% with the ligand **2** system and 28% with (*R*,*R*)-DET (2 equiv per Ti) as the ligand; the yields of sulfoxide were reduced by a factor of ca. 1.5. The enantioselective formation of **1** could also be effected using only 20 mol % **2** and Ti(O-*i*-Pr)$_4$ on a larger scale.[5]

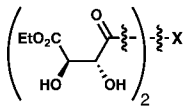
We also examined the application of the **2**/Ti(O-*i*-Pr)$_4$/CHP/H_2O system (1:1:2:1 ratio in CH_2Cl_2 at −20 °C) to a series of unsymmetrical sulfides, and the results are summarized in Figure 4B. In each case, the observed enantioselectivity is higher than that obtained with the optimized Kagan system. It should also be mentioned that the use of the **2**-based reagent has the advantage over DET that efficient recovery of the ligand for reuse is possible because of its ready extraction from the aqueous citric acid[2g] used in workup of the reaction. Oxidations using the ligand **2** system could also be performed at −40 °C and were found to be more enantioselective (e.g., 96% ee for **1**). We are currently investigating other useful applications of ligand **2** to enantioselective catalysis.

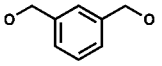
A small series of ligands **5** based on two linked (*R*,*R*)-monoethyl tartrate subunits, which are analogous to tetraol **2**, were synthesized and evaluated for the oxidation of methyl *p*-tolylsulfide to the sulfoxide (Figure 4A). Of these, **5a** was found to be almost as effective as **2** in promoting the reaction enantioselectivity and rate. The effectiveness of the other ligands decreased in the order **5b** > **5c** ≫ **5d**.[5] With ligand **5d**, the sulfoxide was formed under Kagan conditions with only ca. 15% ee, a finding which is easily understandable since this ligand does not allow formation of a structure analogous to **3**.

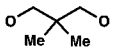
There are a number of reasonable possibilities for the favorable effect of water (or 4 equiv of *i*-PrOH)[2,3] on the enantioselectivity of the Kagan–Modena oxidation of sulfides to sulfoxides: (1) water (or *i*-PrOH) may improve the *P*/*M* helical isomer ratio of Ti(DET)$_2$CHP, with the former isomer but not the latter being on the enantioselective pathway; (2) water may inhibit oxidation via other non-enantioselective paths; and (3) water may increase the rate of oxidation of sulfide via the *P* isomer of Ti(DET)$_2$CHP relative to that via the *M* isomer.[14] A more precise clarification of the influence of water on the enantioselectivity is challenging because of the presence of multiple species in the Kagan–Modena system.[4]

The rate of Kagan–Modena oxidation increases with increasing hydroperoxide and sulfide concentrations when DET is used as the ligand.[5] In the case of the sulfide reactant, the rate dependence is almost but not strictly first order,

A: Variation of the linker, X



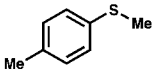
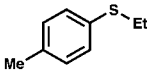
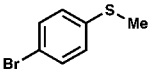
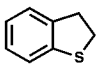
5a, X= 

5b, X= 

5c, X= 

5d, X= 

B: Oxidation of a series of sulfides with ligand 2, Ti(O-*i*-Pr)$_4$, CHP, H_2O for 1h in CH_2Cl_2 at –20 °C[5]

entry	substrate	yield (%)	ee (%)
1		90 Kagan: 79[a]	92 80-86[a]
2		93 Kagan: (71)[b]	84 (74)[b]
3		88 Kagan: (70)[b]	86 (80)[b]
4		89 Kagan: (70)[d]	92[c] (57)[d]

[a]Conversion determined by 1H-NMR analysis after a 1h reaction time; conditions under which methyl *p*-tolylsulfone is not formed. [b]Value in parentheses is that reported by Kagan and co-workers[2b] for extended reaction times. [c]Reaction time was 12h. [d]This experiment was performed by Dr. Rong-Jie Chein – under Kagan conditions for 4h.

Figure 4. (A) Variation of the linker. (B) Comparison to the Kagan process.

possibly because the sulfide can complex to Ti and compete with hydroperoxide for Ti coordination to form an η^2-peroxy complex. Similar inhibition was also observed for DET as the DET/Ti ratio was increased from 2 to 4. The oxidations with **2** as the ligand also showed positive-order kinetics for the sulfide and hydroperoxide.[5]

It is of some interest in connection with the enantioselective Kagan process[15] and the oxidations directed by ligand **2** that the ligand-free oxidation of methyl *p*-tolylsulfide with Ti(O-*i*-Pr)$_4$ and CHP alone in CH_2Cl_2 at −20 °C is much faster and rapidly leads to ca. 2:1 mixtures of racemic sulfoxide and

dx.doi.org/10.1021/ja305991k | J. Am. Chem. Soc. 2012, 134, 17354–17357

sulfone.[2] Thus, the ligands (*R*,*R*)-DET and **2** actually decelerate the ligand-free Ti(IV)-catalyzed process. It is possible that the beneficial effect of water is due to a reduction in the amounts of $Ti(O\text{-}i\text{-}Pr)_4$ or species having just one DET attached to titanium.

In conclusion, the present work has resulted in the development of **2**, a new and highly effective chiral ligand for the enantioselective, Ti(IV)-promoted oxidation of sulfides to sulfoxides, and also a logical pathway for this process. In addition, these studies, together with a careful examination of the Kagan process, have clarified this important but long-mysterious area. Finally, our work has revealed a striking similarity between the enantioselective oxidations with **2** and DET as ligands for Ti as a consequence of parallel mechanistic paths.

■ ASSOCIATED CONTENT

Supporting Information

Optimized *XYZ* coordinates for the *P* and *M* forms of $Ti(DMT)_2(t\text{-}BuOOH)$, Ti(**2**)(*t*-BuOOH), and other Ti complexes; complete ref 11a; full experimental details for oxidation reactions and the syntheses of ligands **2** and **5**; initial rates data; reaction progress kinetic data; and nonlinear effects data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors dedicate this paper to Prof. Henri B. Kagan for his pioneering contributions to asymmetric synthesis. This work was supported by Bristol-Myers Squibb (postdoctoral fellowship to T.R.N.), Zhejiang University (cooperating research fellowship to X.L.), the Hertz Foundation (graduate fellowship to M.M.B.), and the Harvard Undergraduate Research Program (C.M.C.W.). Dr. R.-J. Chein is gratefully acknowledged for a sample of dihydrobenzothiophene and for data on its oxidation.

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(5) See the Supporting Information (SI) for details.

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(12) The energy of the *P* diastereomer was also found to be lower than that of the *M* diastereomer using the M06-2X/6-31G*//LANL2DZ procedure, the difference being somewhat greater than the values reported above.

(13) The procedures used in our work for DFT satisfactorily reproduced the bond lengths and angles of the Ti—hydroperoxide complex described in the X-ray analysis of Boche et al.[8] Additionally, the extent to which the tertiary alkyl group of the peroxide is out of plane is closely reproduced (see the SI for details). This deviation from planarity has a through-space steric effect on the conformation of the neighboring five-membered tartrate titanacycle. This secondary interaction helps to explain the increase in ee associated with replacing *tert*-butyl hydroperoxide by CHP in the Kagan oxidation.

(14) A Swedish group[9] has described evidence that H_2O can also favor the formation of monomeric Ti species from dimeric O-bridged structures.

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