

# SEARCHING FOR NEW REACTIVITY\*

Nobel Lecture, December 8, 2001

by

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In 1938, three years before I was born, a live coelacanth was taken from the waters off the eastern coast of South Africa. Previously known only in the fossil record from some hundred million years ago, the coelacanth and the implications of its discovery remained big news for years, fueling an enthusiasm for “creatures” that persisted for decades. Those of us born in the Forties grew up on photos of eminent scientists setting off on expeditions, their sunburnt faces dwarfed by mountain explorer’s garb, or making thumbs-up signs as they entered the water in scuba gear. We shared their confident expectation that the Loch Ness Monster, Sasquatch, the Yeti – even a dinosaur – soon would be taken alive.

I grew up loving the sea and loving fishing in particular, but unlike most fishermen I cared less for the size or quantity of the catch than for its rarity. Nothing could be more exciting than pulling (if not this time, surely the next!) a mysterious and hitherto unknown creature from the water. As a kid, I passionately wanted to be one who caught the next coelacanth, the first to see something that was beyond reasoning, even beyond imagining.

Opening a Nobel Lecture with a fishing expedition may seem frivolous, even indecorous, but I assure you no disrespect is intended. These are the circumstances that shaped my professional life: my first laboratory was New Jersey’s Manasquan River, whose astonishingly rich variety addicted me to discovery; a few years later, when I was as comfortable at sea as I’d been on the river, my laboratory became the Atlantic Ocean; later when I started doing chemistry, I did it the way I fished – for the excitement, the discovery, the adventure, for going after the most elusive catch imaginable in uncharted seas.

Chemists usually write about their chemical careers in terms of the different areas and the discrete projects in those areas on which they have worked. Essentially all my chemical investigations, however, are in only one area, and I tend to view my research not with respect to projects, but with respect to where I’ve been driven by two passions which I acquired in graduate school: I am passionate about the Periodic Table (and selenium, titanium and osmium are absolutely thrilling), and I am passionate about catalysis.

\* Adapted with the permission of the editors from “Coelacanth and Catalysis”: K. B. Sharpless, *Tetrahedron* **1994**, 50, 4235.

What the ocean was to the child, the Periodic Table is to the chemist; new catalytic reactivity is, of course, my personal coelacanth.

Even though I grew up in Philadelphia, if someone asks me where I'm from, I usually say "the Jersey Shore," because that's where my family spent summers, as well as many weekends and holidays, with my father joining us whenever he could. My father had a flourishing one-man general surgery practice which meant he was perpetually on call. With him at home so little and practically guaranteed to be called away when he was, my mother liked being near family and friends at the Shore, where her parents had settled and established a fishery after emigrating from Norway. When I was a baby, my parents bought land on a bluff overlooking the Manasquan River about four miles up from where it enters the Atlantic.

Like many scientists I was a very shy child, happier and more confident on my own, and my interest was totally absorbed by the river. In those days, the incoming tide transformed our part of the river from a channel flanked by broad mud flats to a quarter-mile basin that exploded with life of myriad variety – about a dozen kinds of fish big enough to make it to the dinner table, plus blue crab, eel, and a bounty of fry and fingerlings that would graduate downstream to the ocean. I was obsessed with finding and observing everything that lived in the river and knowing everyone who worked on it.

My most delicious childhood memory is the excitement I experienced at the instant of awakening almost every summer morning. The sound I associate with that feeling is the distant whine of my first scientific mentor's outboard motor. That was my wake-up call, and within minutes I was at river's edge, waiting in the pre-dawn stillness for Elmer Havens and his father Ollie to make their way across the river from Herbertsville to pick me up to "help" them seine for crabs. Amused by my regularly walking along the bank to watch them haul their seine, Elmer eventually installed me in the boat, which he used for transportation as well as for steadying himself as he dragged the seine's deep-water end. Ollie walked one end of the seine along the shore, alarming the crabs gathered at the river's edge, and frightening them toward deeper water and so into the net's pocket. Chest deep in water and mud, Elmer walked parallel to his father, one arm clasping the seine, the other hooked over the boat's gunwale. Elmer and I, our heads close together, would speculate about the catch, taking into account all the variables – the weather, the season, the tide. Every hundred yards or so, Elmer doubled ahead toward the shore to draw the purse. I liked it best if a big eel or a snapping turtle got caught up in the net, making the water boil and the net flop into the air. I always hoped we'd catch something new.

I had a little dinghy, and my realm of exploration expanded in direct proportion to my rowing ability. But the same tide that created this abundant estuary also was my nemesis, forever stranding me upriver in the narrows or perhaps at Chapman's Boat Yard, a mile downstream and on the opposite bank. Since my parents couldn't keep me off the water, they opted for increasing the likelihood of my getting home unaided by giving me a boat with an outboard. It wasn't long before I went down river all the way to the inlet

(absolutely forbidden, of course), and, soon after, the prospect of new creatures to pull from the water lured me out through the rock jetty and into the ocean; at the time I was only seven or perhaps eight years old.

By the time I was ten, I ran crab and eel traps and supplied everyone we knew with fish as well; at fourteen I started working during the summer as the first (and only) mate on a charter boat. My parents allowed me to go to sea when I was so young and small even for my age because I was offered a job on a relative's boat – little did my parents or I know that Uncle Dink, a cousin actually, offered me the job so he wouldn't have to pay a “full-sized” helper. I so wanted to keep working on the boats that it was years before I dared tell my parents what went on aboard the Teepee, like how the Coast Guard refused assistance to Dink because his boat was in chronic disrepair. (Consequently, some of our adventures at sea were memorable indeed – grappling hooks and guns have their place in the canon – and I mention this trove of Uncle Dink stories because for years my MIT colleagues begged me to tell them over and over again.)

On a charter boat the captain pilots the ship and finds the fish the customers reel in. Meanwhile, the mate is over the boat like a dervish, skillfully arraying the water with fishly temptations – adjusting outriggers, finding the perfect combination of lure or bait and tackle, always mindful of the action on nearby boats competing for the same fish.\* Since my friends were all mates we naturally agreed that enticing fish to bite was the greatest challenge, but I alone felt that getting the strike was the most fun, even more exciting than landing the fish. I worked as a mate almost daily every summer, right up until the day before I set out from New Jersey headed toward the biggest ocean and graduate school at Stanford University.

That was in 1963. In the spring of that year my inspiring Dartmouth College chemistry professor and first research director, Tom Spencer, talked me into delaying entering medical school to try a year of graduate school. He sent me to Stanford specifically to work for E. E. van Tamelen, Tom's own mentor at Wisconsin. The appeal of fishing was such that Tom, to my later regret, never succeeded in getting me to spend any summers working in his lab. In fact even in graduate school I expressed my ambivalence by continuing to fantasize about finding a boat out of Manasquan to skipper and by failing –

\*This diversion into fishing-as-metaphor-for-research could go on for pages: consider how when a boat was hooking tuna – the catch of choice – word spread by radio and the competition converged from every compass point. The hot boat's captain greeted this acknowledgment of his success with some anxiety: while he liked setting the other captains' agendas and pleurably speculating that the parties on the other boats were considering chartering him next time, the secrets of his success nonetheless required protection, so trolling speeds were lowered to sink the lures and prevent rubbernecks from identifying them, and red herrings (literally, on occasion!) were casually displayed on the fish box. Isaak Walton and John Hersey devoted whole books to this metaphor, so indulge me for a few more sentences. The handy process vs. product dichotomy that applies so neatly to much of human endeavor illuminates this fisherman-chemist comparison, too. Conventional wisdom places fly-fishing at the “process” end of the scale, while a “product” fisherman uses sonar to find a school before he bothers to get his line wet. Process person though I am, only the Manasquan River ran through my fishing days: trolling for the unknown always had more appeal than hooking a trout I already knew was there.

this did not please v.T. – to do the simple paperwork required to renew my NSF predoctoral fellowship.

However, toward the end of my first year at Stanford, a serendipitous misunderstanding catalyzed the complete transfer of my passion (some would say my monomania) from one great science to another, from fishing to chemistry. Before leaving for a lengthy European visiting professorship, v.T. sent me to the library to look for reactive inorganic species that might produce interesting transformations of organic compounds. My first projects with v.T. were selective oxidation of polyolefins and titanium-mediated deoxygenative coupling of alcohols, and I was already primed to appreciate useful chemistry employing “strange” elements after selecting the Wittig Reaction from a list of suggested topics for my student seminar. The Wittig Reaction really engaged my enthusiasm, and I ingenuously concluded that finding new reactions other chemists could use looked like a lot of fun.

In any event, upon v.T.’s return, I discovered he had not intended for me to spend all those months immersed in the literature. While I had no research results to report, I did have a notebook filled with ideas and an eagerness to drop my line throughout the vastness of the Periodic Table. I don’t think I’ve gone fishing in the literal sense a dozen times since then!

From van Tamelen, a Gilbert Stork protégé, I inherited enthusiastic disdain for “safe” problems, deep admiration for traditional multistep organic synthesis, and awe before selective biological catalysis: studying the squalene oxide/lanosterol cyclase enzyme left me impressed by enzymic selectivity but depressed by the difficulty of using enzymes for synthetic transformations. After getting a double dose of him in the classroom, Derek Barton became my model. At Dartmouth Tom Spencer taught a course on conformational analysis based on one he took at Wisconsin from William S. Johnson (Tom’s uncle, in fact), then I experienced the original at Stanford.\* Being wet behind the ears, I took conformational analysis for granted: it was Sir Derek’s search for new reactivity that electrified me. A postdoc with Jim Collman (the only person, I concede, who gets more excited about chemistry than I do) ignited my interest in using simple metal complexes to develop catalysts (in the Collman lab, incidentally, I had the privilege of many hours at the blackboard with labmate Bob Grubbs). Then, before taking up my job at MIT, a postdoc with Konrad Bloch confirmed my hunch that impatience rendered me incompetent around enzymes. Konrad graciously let me start working on my own ideas when his proved much too frustrating for me.

One other part of my background seems to have contributed to my chemistry. The first American Sharpless (“Sharples” then) came to Pennsylvania in the Seventeenth Century, not long after William Penn. My father was a prac-

\* When teaching MIT undergraduates I always said, “The lights came on with conformational analysis,” without thinking where I picked up the phrase, but now I know: the previous Tetrahedron Prize article states, “Just as chemists of the Robinson generation worked without concern for stereochemical factors so we, in the early days, were working in ignorance of conformational considerations until Derek Barton showed us the light in 1950.” The author is, of course, Bill Johnson (see reference 1).

ticing Quaker only as a child, but the values in our home were Quaker values, and I was educated in a Quaker school. The Quakers encourage modesty, thrift, initiative, and enterprise, but the greatest good is being a responsible member of the community – being useful. “Elegant” and “clever” were the chemical accolades of choice when I started doing research, just as “novel” is high praise now. Perhaps the Quakers are responsible for me valuing “useful” most.

So that is my background as a chemist. I’ve been accused of going too far when I speculate that chirality fascinates me because I handled my umbilical cord in utero, but I’m quite sincere in proposing that the extraordinary training I received as a young chemist transformed an existing passion for discovering the unknown into the search for new reactivity, and that Quaker utilitarianism made the selective oxidation of olefins so appealing.

With respect to chemical reactions, “useful” implies wide scope, simplicity to run, and an essential transformation of readily available starting materials. Clearly, if useful new reactivity is the goal, investigating the transformations chemists rely on is the obvious strategy. The processes for the selective oxidation of olefins have long been among the most useful tools for day-to-day organic synthesis because of these appealing characteristics of olefins:

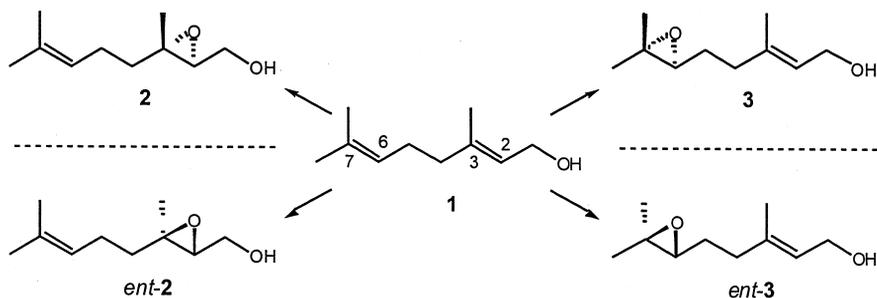
- they are among the cheapest functionalized organic starting materials,
- they can be carried “hidden” through conventional acid/base-catalyzed transformations, then “revealed” at will by adding heteroatoms through selective oxidations,
- most simple olefins are prochiral, providing a prominent portal to the chiral world.

The trisubstituted olefin geraniol, in addition to being one of my favorite smells, provides an excellent case study both for laying out the challenges of selective olefin oxidation as well as for noting some benchmarks in meeting those challenges.

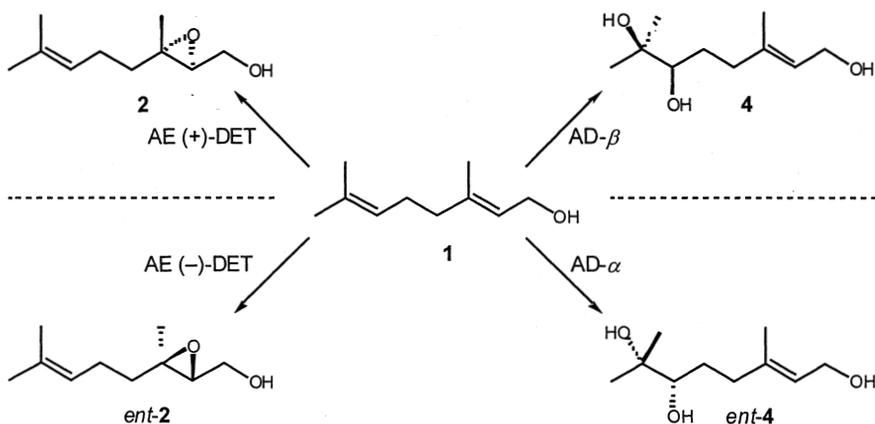
As shown in Scheme 1, geraniol (**1**) has two trisubstituted olefinic units, one of which has a hydroxyl in the allylic position. Four monoepoxides are possible: making either racemic **2** or racemic **3** requires regio- (or chemo-) selectivity, while making each of the individual enantiomers requires enantioselectivity. When Henbest showed that the electronic deactivation by the oxygen substituent at C-1 causes peracids to prefer the 6,7-double bond (especially on the ester derivatives), making racemic **3** became possible.<sup>2</sup> When I started doing research in the Sixties, neither racemic **2** nor any of the enantiomers could be synthesized directly. Solving the other half of the regioselectivity problem was an obvious challenge, but enantioselectivity was considered well-nigh impossible.

In 1973, Bob Michaelson cracked the other half of the regioselectivity problem presented by geraniol.<sup>3</sup> Since early-transition-metal-catalyzed epoxidations with alkyl hydroperoxides proved highly selective for the 2,3-position, racemic **2** could be prepared as well.

In 1980, Tsutomu Katsuki discovered the titanium-catalyzed asymmetric



Scheme 1. Regio- and enantioselective monoepoxidations of geraniol.



Scheme 2. Asymmetric epoxidation and dihydroxylation reactions of geraniol

epoxidation (AE); the enantioselective oxidation of olefins bearing allylic hydroxyl groups made it possible to make either **2** or *ent-2* thus solving one side of the enantioselectivity problem.<sup>4</sup>

The osmium-catalyzed asymmetric dihydroxylation (AD), discovered in 1987, subsequently was improved to the point that either **3** or *ent-3* could be made by way of the diol, an indirect solution to enantioselective epoxidation at the 6,7-position (Scheme 2).<sup>5</sup>

In 1990, came the breakthrough introduction of enantioselectivity into existing manganese salen ligand catalysts for the epoxidation of isolated olefins.<sup>6</sup> Developed independently by the groups of Jacobsen<sup>6a, 10</sup> and Katsumi<sup>6b</sup>, these epoxidation catalysts work best on only a few of the six olefin-substitution classes. Nonetheless, their very existence is tantalizing, encouraging the hope that a general, off-the-shelf solution will be found for the direct asymmetric epoxidation across the full range of isolated-olefin substitution patterns.

The greater generality of man-made catalysts, such as these, compared with enzymes was noted first by Knowles<sup>7a,c</sup> and Kagan.<sup>7b</sup> During the lean times in the first decade of my career, their pioneering development of man's first highly enantioselective catalysts (the L-dopa synthesis that came out of

Knowles' Monsanto lab was the asymmetric hydrogenation's first commercial application) sustained my faith that a catalyst for asymmetric oxidation could be found. Jack Halpern's mechanistic studies<sup>7d</sup> on asymmetric hydrogenation catalysis likewise inspired me. Several Japanese chemists, chief among them Ryoji Noyori,<sup>7e</sup> hugely extended both the scope and application of the asymmetric hydrogenation process<sup>8</sup>.

This focused search has frustrated but never bored me even after so many years, and the geraniol paradigm illustrates why. My own investigations into the oxidation of olefins commenced at MIT in 1970, but, fittingly, I was back at Stanford on January 18, 1980, for Tsutomu Katsuki's dramatic discovery of the titanium-catalyzed asymmetric epoxidation.<sup>4, 9a</sup> Two years later the most scientifically stimulating and professionally gratifying collaboration of my career, the total syntheses of the eight L-hexoses with my MIT colleague Sat Masamune, capped the AE's discovery.<sup>11</sup> Previous articles<sup>12</sup> in a vein similar to this one describe that chemistry; understanding the AE's significance and putting that understanding to work are the purview here.

After the euphoria of completing the hexose syntheses, three years were spent developing, refining, and finding more applications for the AE. During this time I returned to the search for new reactivity, but it was clear that my random, scattershot attempts were going nowhere,\* so I was grateful for the

\* I have enormous admiration for colleagues who can keep multiple research projects alive and large groups humming, but the "monomania" that prevents me from being able to do that is my long suit as well, making it possible to concentrate – for years, actually – on a single topic. I know some chemists call my approach "intuitive," a term I've always thought underestimates the rigor that frames my method; perhaps "unstructured" or "contemplative" is more accurate. Many of my cohorts are quick and facile and can jump on a few interesting bits of data and start building tentative edifices that get taken apart and reassembled to suit new data. I, on the other hand, am ruminative: my training after all consisted of busily poking and perturbing the Manasquan River, a curriculum both urgent and leisurely, one that permitted exploration without assumptions and without the structure imposed by deadlines or competition or by knowing too little or too much. Since I was compelled by shyness to learn to do much on my own, there was (and is) no right or wrong way, only many ways, some more or less suited to a given endeavor. The discipline, nonetheless, is exacting: everything that can be observed should be observed, even if it is only recalled as the bland background from which the intriguing bits pop out like Venus in the evening sky. The goal is always finding something new, hopefully unimagined and, better still, hitherto unimaginable. When I became a bench- and desk-bound explorer the method stayed the same. I try to imagine away the packaging information arrives in, then let bits and pieces move around lazily, rather like objects tumbling slowly in zero gravity, but eventually, over time, exploring every possible relationship with other information that's previously arrived. Since joining the faculty of The Scripps Research Institute, I've discovered that ocean swimming and running on the beach provide an excellent medium for this kind of activity; however, in any climate the best catalyst is generous, stimulating conversation. This slow but endlessly fascinating method is like an exotic ritual courtship, full of displays of bright feathers or offerings of shiny metal or towers of sticks – what does it all, what does any of it mean? Enormous concentration is required to remember it all in a way that causes little sparks when certain conjunctions appear, making a connection with something noted previously, perhaps decades ago. Sadly, as I grow older, the connections become harder to summon up, so the sparks, though seeming as bright as ever, are less frequent. I describe this process at length because it's not the way most scientists approach their work, nor is it well suited to the demands of funding agencies that are railroaded into answering questions posed for political rather than scientific reasons, nor to the needs of graduate students who require publications to compete for jobs. Academic chemistry is much harder now, and I'm glad I was born when I was.

opportunity to spend the first three months of 1987 as a Sherman Fairchild Scholar at Caltech.

Many universities and institutions have handsome Fairchild buildings, but Caltech, ever the bastion of collegiality and camaraderie, used its Fairchild grant to endow a program that brings scientists from many fields to be housed graciously in the sunshine for as long as a year. Since my research group's investigation of the AE had reached the point of diminishing returns, I left for Pasadena hoping to renew my mission.

I love reading journals, and I love mountains, so the Caltech library with its panoramic view of Mt. Wilson became my thinking place of choice. Every day Mt. Wilson offered new vistas, especially on those occasions when snow fell during the night. One morning the mountain was completely cloaked (the first time a freezing temperature was recorded in downtown LA, I recall), and the melting snow receded at such a clip I was sure I saw it happening. Mt. Wilson was the perfect backdrop for bringing my own big picture back into focus, and I returned to MIT eager to renew my search for new reactivity. Meditating on the AE yielded this lesson to guide that search:

ligand-accelerated catalysis (the significance of which is documented in M. G. Finn's fine MIT thesis on the mechanism of the AE<sup>13</sup>), is crucial to the AE and not merely a feature of it; despite its rarity this phenomenon might be the agent for uncovering more catalytic processes.

Of course, the first and best-known example of ligand acceleration is found in Criegee's papers from the Thirties.<sup>14</sup> He observed that pyridine accelerates the reaction in his classic study of osmium tetroxide and olefins. Ironically, the lesson from the AE was directing me back toward Criegee, whose discoveries in olefin oxidation and osmylation were, in large measure, the jumping off point for my own research career.

I first looked into Criegee's process shortly after becoming an assistant professor at MIT. My attraction to the reaction of OsO<sub>4</sub> with olefins was inevitable. Osmium tetroxide not only accomplishes an important synthetic transformation, but it does so with a scope and reliability unique among reactions used for organic synthesis. It reacts only with olefins and it reacts with all olefins (slight poetic license here). Even R. B. Woodward valued Criegee's stoichiometric transformation so much he was willing to use 100 g of OsO<sub>4</sub> in one shot. Osmium's expense was not compatible with "useful," however and, since the existing catalytic variants were not very effective, I started searching for a reliable catalytic method. In 1975 Kagayasu Akashi found a good process for us based on a hydroperoxide as oxidant, *tertiary*-butyl hydroperoxide (TBHP)<sup>15</sup>, but the brass ring was ultimately captured that same year with the publication of the famous Upjohn process based on *N*-methyl morpholine-*N*-oxide (NMO).<sup>16</sup>

Throughout the rest of the Seventies osmium remained our primary tool for looking for new reactivity: we discovered that imido osmium(VIII) species effected stoichiometric *cis*-oxyamination of olefins in direct analogy to the *cis*-dihydroxylation of olefins by osmium tetroxide; even more effective catalytic versions of those transformations came shortly thereafter.

In 1977, I left MIT, where I had been a contented member of a wonderful chemistry faculty since 1970, for Stanford University, where I previously spent six contented years as a graduate student and postdoc, surrounded by a wonderful chemistry faculty. I never made the transition back to contentment at Stanford, probably because my research wasn't churning up much. This frustrated me and scared off potential graduate students who wanted publications, not a fishing expedition. In addition, at Stanford I remained awed by a faculty I worshiped when a graduate student, and I lacked the confidence to stand firm on issues, particularly faculty appointments, that meant a lot to me. In 1979, at about the same time I made the decision to return to MIT, Steve Hentges, who worked in our well-developed osmium imido area and already had the material for a good Ph.D. thesis in hand, decided to take on one more project before writing up.

The notion of an asymmetric ligand for osmium tetroxide had been knocking around the lab for years, and Steve first approached the idea by making several pyridines with chiral substituents at the 2-position; these gave diols with essentially 0% *ee*!<sup>17</sup> Pyridine is only a modest ligand for osmium tetroxide, and, as we discovered, any *ortho* substituent is lethal to binding. But since William Griffith at Imperial College had shown that quinuclidine binds much more strongly to OsO<sub>4</sub>, I suggested trying the cinchona alkaloids, essentially substituted quinuclidines.<sup>18</sup> (Many chemists have expressed surprise at how quickly we arrived at what is now the best ligand framework for the AD: anyone with a natural products background and who is also a fan of Hans Wynberg's chemistry recognizes the cinchona alkaloids as the obvious next step.) The results were spectacular, even without taking into account a measurement error (discovered years later) that caused most of the *ee*'s to be underreported by 5 to 15%!<sup>17</sup>

Steve had a dramatic story to cap his thesis work, so he started writing; my attention was taken up by the decision to return to MIT. Then, a couple of months later, Katsuki discovered an asymmetric process with ingredients so cheap it made working with osmium look like Rolls-Royce chemistry. Although the AE was only weakly catalytic in the early days,<sup>19</sup> its uniformly high *ee*'s and nontoxic, inexpensive reagents were enough to completely divert our attention from its promising but stoichiometric predecessor, the OsO<sub>4</sub>/cinchona asymmetric dihydroxylation.

The preceding paragraph has no doubt failed to deflect your attention from the obvious question: Why didn't I try the Hentges ligands in the Upjohn system in 1979? Indeed, why did I propose the experiment in my NIH grant renewal in January, 1984, but not follow up on it? "As for the ligand," I wrote in the proposal, "it is probably best to stay with the cinchona derivatives because the quinuclidine moiety is the best ligand we know of for Os(VIII) complexes. The substrate will be stilbene... the osmium catalyst will be recycled using an amine *N*-oxide. Ideally, both the osmium and the chiral alkaloid could be used in catalytic quantities. A successful system of this type could be of great practical importance."

Instead of poking and perturbing, the Jersey Shore School of Thinking's

Sc	<b>Ti</b>	V	Cr	Mn	Fe	Co	Ni	Cu	Zn																	
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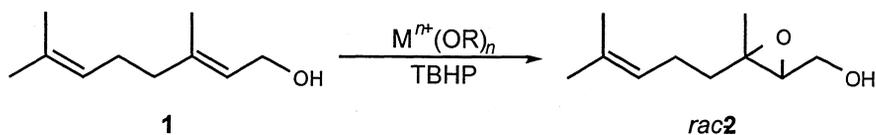


Figure 1. Metals Catalyzing the Epoxidation of Allylic Alcohols by TBHP. Adding tartrate ligand always affects reactivity: the titanium system is accelerated.

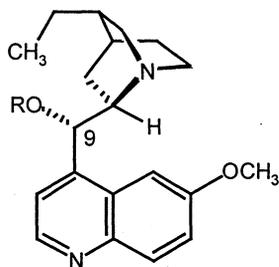
cardinal rule, I stuck with the odds logic suggested: ligands accelerate the reaction of  $\text{OsO}_4$  with olefins, but they also bind avidly to the resulting osmate ester, lethally effecting catalyst turnover. This ability of ligands such as pyridine and quinuclidine to kill turnover in catalytic osmylation systems had been often observed in my laboratory. What I did not, nor could not, anticipate is the perfect balance cinchona alkaloids achieve in ligating ability, binding well enough to accelerate the key step, but weakly enough to slip off allowing the hydrolysis/reoxidation steps of the catalytic cycle to proceed. At the time, however, the precedents seemed clear, so the AD languished until 1987.

Unraveling the mechanism of the AE was largely the work of M. G. Finn.<sup>13</sup> His persistent exploration during the early- to mid-eighties of the AE's titanium-tartrate catalyst system exposed a complex mixture of species in dynamic equilibrium with one other.<sup>20</sup> M. G. discovered the main species  $[\text{Ti}(\text{DIPT})(\text{O-}i\text{Pr})_2]_2$  is substantially more active than the many other species present (significantly, it is five to ten times more active than  $\text{Ti}(\text{OR})_4$ , a catalyst for the formation of racemic epoxy alcohol) and this rate advantage funnels catalysis through the appropriate tartrate-bearing species.

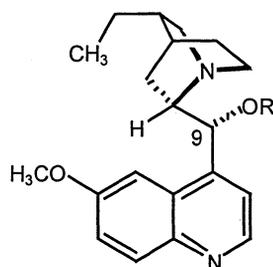
If the tartrate-induced acceleration of the titanium-catalyzed epoxidation reaction came as a surprise, investigating that phenomenon brought even more surprising results. We ultimately found twenty-four metals other than Ti that catalyze the epoxidation of allylic alcohols by TBHP (Figure 1), but all these systems were strongly inhibited or killed by adding tartrate!<sup>21</sup> Ligand-decelerated catalysis was clearly the rule while ligand acceleration was the extraordinarily valuable exception.

Shortly before I left for Caltech, Chris Burns, encouraged by Pui Tong Ho, presciently lobbied to resurrect the  $\text{OsO}_4$ /cinchona asymmetric dihydroxylation, and, without any encouragement from me, I must admit, he embarked on the synthesis of a stoichiometric C3-symmetric ligand for the AD.<sup>22</sup> A few

months later, I, too, was recommitted to osmium, and when Bill Mungall and Georg Schröder reexamined the work from 1979 they uncovered  $\epsilon$ 's even better than previously reported. Meanwhile Eric Jacobsen attacked the problem from the mechanistic side, discovering that the ligand-dependent rate accelerations could be enormous.<sup>23</sup>



dihydroquinidine derivatives



dihydroquinine derivatives

With these very encouraging results on the stoichiometric reaction just in, Istvan Markó joined the project. I was travelling at the time, and on his own initiative, unaware of the NIH proposal, he combined Hentges' system<sup>17</sup> with the reliable Upjohn NMO-based catalytic osmylation system,<sup>16</sup> immediately getting results indicating the reaction was catalytic.<sup>24</sup> However, unlike the dramatic "Eureka!" that accompanied the discovery of the AE, cautious optimism was the response to the catalytic AD and its initially modest  $\epsilon$ 's. Now, however, after years of research since Markó's first experiments in October of 1987, the AD's utility rivals and often surpasses the AE's.<sup>9</sup>

Unlike the AE, for which Katsuki's initial tartrate ester ligands have yet to be eclipsed, the ligands for the AD have evolved substantially in effectiveness and scope through substitution at the C-9 hydroxyl.

The simple ester derivatives (e.g. the acetate and *para*-chlorobenzoate esters) gave way in 1990 and 1991 to aryl ether derivatives, first proposed by Yun Gao during a late night group meeting to address the mechanistic question of a possible ligating role of the ester carbonyl. Brent Blackburn made the phenyl ether which, to our surprise, gave good  $\epsilon$ 's, but was too hard to make to be competitive with the then dominant *para*-chlorobenzoate (CLB) ligand.

Almost a year later Declan Gilheany correctly predicted that aryl ethers should be better for aliphatic olefins than the CLB ligand,<sup>25</sup> and these results laid the foundation for a steady expansion of this ligand class, culminating in the phenanthryl ether ligand.<sup>26</sup> Another big jump in effectiveness came with the dimeric alkaloid ligands having a phthalazine core, first made by Jens Hartung in 1990.<sup>27</sup> Along with the pyrimidine ligands<sup>28</sup> whose development they inspired, they remain the best general ligands for the AD reaction.

The search for better ligands was paralleled by advances in catalyst turnover efficiency:

John Wai found both the second-catalytic-cycle problem and its partial remedy, slow addition of the olefin,<sup>29</sup>

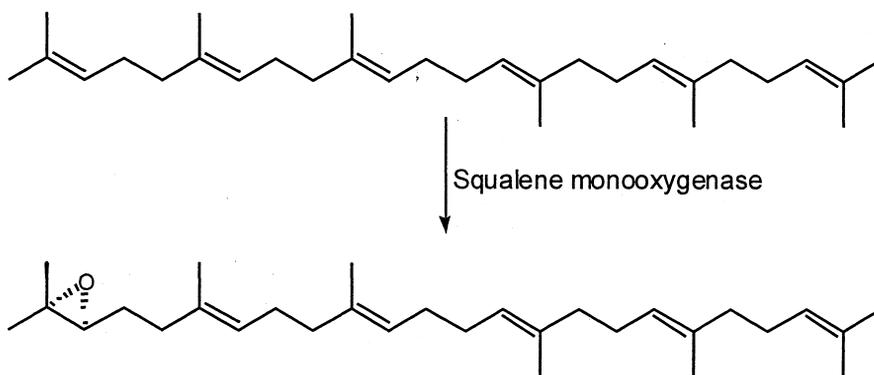
Since ferricyanide in *tert*-butanol/water provides an excellent two-phase system for catalytic osmylation,<sup>30</sup> Hoi-Lun Kwong applied it to the AD, solving the second-cycle problem and the need for slow addition,<sup>31</sup>

Willi Amberg found that adding organic sulfonamides greatly facilitates the rate of catalyst turnover for olefins whose osmate esters resist hydrolysis.<sup>27</sup>

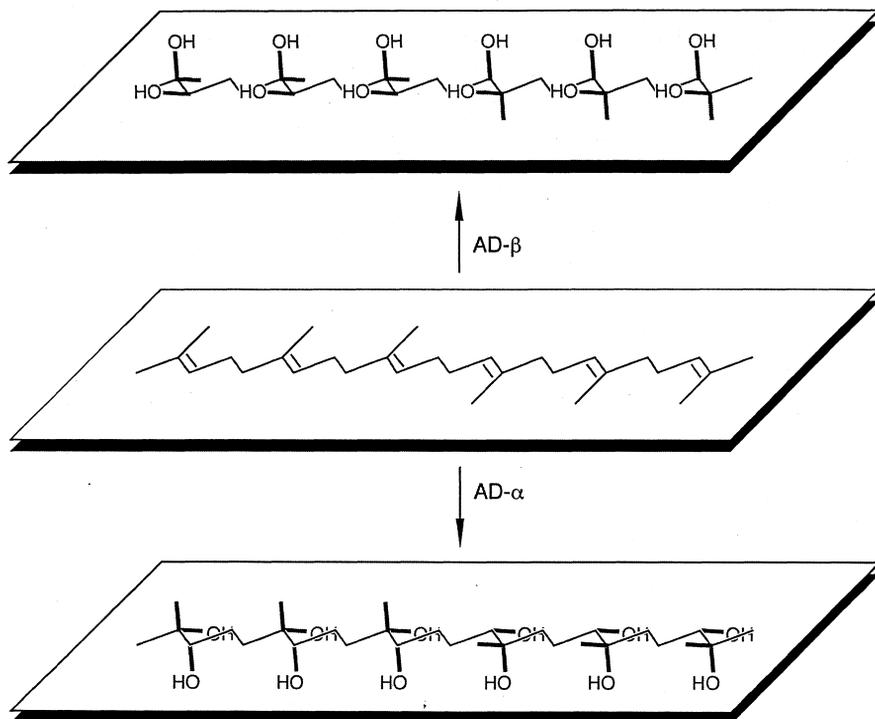
As the practicality (it has been scaled up to run in 4000 liter reactors with no ill effects on yield or *ee*<sup>32</sup>) and scope of the AD process grew, so did the pressure to understand the origin of its enantioselectivity. Mechanistic studies dating from the early Seventies by Alan Teranishi and Jan Bäckvall<sup>33</sup> were rekindled by Eric Jacobsen in 1987 and continued into the mid-90's.<sup>34</sup>

While a complete and general solution to the geraniol paradigm's final challenge is clearly within reach, comparing selectivity at the bench with selectivity in living systems remains striking. For example, the squalene monooxygenase in our livers unerringly deposits a single oxygen atom on the squalene molecule and, in so doing, further chooses only the *si*-enantioface of the terminal double bond (Scheme 3).<sup>35</sup> On the other hand, the attempted AD of a single double bond of squalene does give the terminal diol in 96% *ee*. The preference for the terminal double bond is slight, however, and internal diols as well as tetraols also can be isolated from the reaction.<sup>36</sup> Thus, while the AD catalyst cannot match the exquisite selectivity of the enzymic system, this very inability to discriminate between the six trisubstituted double bonds of squalene allows the exhaustive AD of squalene (Scheme 4) in an overall yield of 79.8% for the AD- $\beta$  reaction.<sup>37</sup>

Serial multistep reactions such as these are generally stymied by Bob Ireland's "arithmetic demon" – the geometric fall in yield in sequential chemical reactions. The AD of each double bond is one step in a procession of six dihydroxylations, each with a chemical and an optical yield, twelve yields in all. Thus the average yield of each step is  $(0.798)^{1/12}$  or 98%, translating to 98% for each chemical yield, 96% *ee* for the single enantioselective reaction and 96% *de* for each of the five diastereoselective reactions. The high yield of a single enantiomer from the multiple hydroxylation events required to com-



Scheme 3. Enzymatic epoxidation of squalene.



Scheme 4. Exhaustive, stereoselective dihydroxylations of squalene.

pletely oxidize squalene reflects the reliability and selectivity of the AD process. Joel Hawkins' Berkeley lab kinetically resolved the chiral fullerene  $C^{76}$  resulting in the first enantiomerically pure allotrope of carbon, the AD's most intriguing use to date.<sup>38</sup>

My decision, nearly twenty-five years ago, to study the selective oxidation of olefins produced an unexpected bonus, one that gave me an opportunity to investigate uncharted territory on a scale that is more associated with the previous half-century than with our own. Selenium, titanium/alkyl peroxides, and osmium, my three most successful olefin oxidation catalysts, all had phobias associated with them, with the result that much of their chemistry remained *terra incognita*. Selenium and osmium were considered highly toxic, and the peroxide oxidants used with titanium had a nasty reputation. Rarely did I find myself in another chemist's territory; likewise, few wanted to cast a line in mine.

Tracking these elements offers a rather curious way to view my research. Figure 2a plots the time course of their dominance (as measured by publications for want of a more qualitative ruler) during the years 1970–1993. Selenium came first, flourished, then ended abruptly. Osmium research came next, co-existing with selenium until both were eclipsed by titanium, the descendant of molybdenum and vanadium. Osmium made a strong comeback, knocking off titanium.

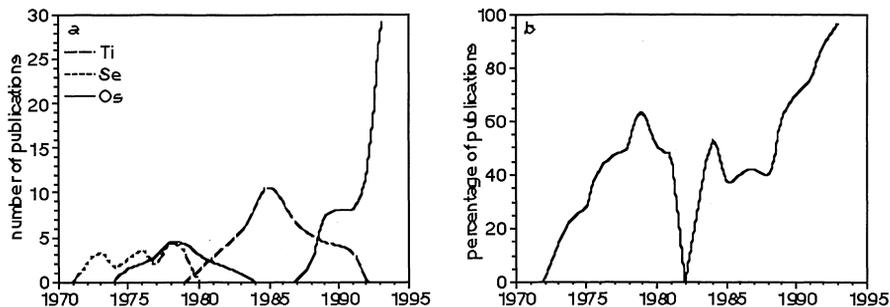


Figure 2. (a) Selenium, titanium, and osmium chemistry; note the osmium line's bimodality. (b) Growth of Catalysis in my laboratory.

Figure 2b, charting my research with respect to catalytic transformations, looks quite unlike Figure 2a, but relates directly to it. As my involvement with catalysis grew, the largely stoichiometric selenium reagents lost their appeal; titanium fell because the effectiveness of the titanium catalyst for the AE is modest, with about only twenty turnovers per titanium center before all activity is lost. Osmium, despite a bimodal presentation, was never actually out of the picture, merely quiescent until the discovery of the highly catalytic AD (it has been run to completion with as little as 1/50,000 of osmium catalyst).

In Figure 2b the only real defection from the steady growth of catalysis to dominion in my research was the 1982 trough caused by the hexose synthesis collaboration with Sat Masamune. Stepping out of the realm of catalysis is almost unimaginable to me now.

Because of its unique potential for channeling a reaction sequence along one of myriad possible pathways, selective catalysis lies at the heart of both pure and applied chemistry, not to mention life chemistry. In addition to the selectivity benefits of catalysis, the phenomenon of turnover (which equals amplification), implicit in the definition, highly leverages its potential impact. For all these reasons, catalysis was and continues to be the engine driving my research.

Nature's enzymes made it possible to imagine simpler asymmetric catalysts. What we found, however, was unimaginable on two scores: small, highly enantioselective catalysts that were not only not fettered by nature's "lock-and-key" modus operandi, but tolerant as well of substrates throughout the entire range of olefin substitution patterns. Now, going on four decades later, I am still plumbing the vastness of the Periodic Table in search of new catalytic reactivity. The unpredictability and rarity of what I seek are not deterrents since I am, after all, the product of optimistic times. There are other coelacanths to be found!

## ACKNOWLEDGEMENT

Above all I thank and express my deep gratitude to my past and present coworkers at MIT, Stanford and The Scripps Research Institute. Many of you learned to tolerate my style of directing research (an oxymoron perhaps?); in-

deed, some of you flourished. Others were not well served, and to you I sincerely apologize. I'm exceedingly proud of the MIT undergraduates who got their feet wet in my lab and now hold leading academic and industrial positions: remember you got your opportunities because Tom Spencer gave me mine and I expect you to do the same. Mentioning Tom brings me back, as so many things do, to E. E. van Tamelen: the bright flashes of his career remain of the first magnitude and still inspire me. And finally, my scientific career would have been unthinkable without the constant support and counsel of my wife, best friend – and ghost writer – Jan.

I also thank the National Institute of General Medical Sciences, National Institutes of Health (GM-28384) and the National Science Foundation for their continuous financial support over the past twentyfive years, and, more recently, the W. M. Keck Foundation and the Skaggs Institute for Chemical Biology for helping to make possible my present tenure at The Scripps Research Institute in La Jolla.

## REFERENCES AND NOTES

1. Johnson, W.S. *Tetrahedron* **1991**, 47, xi-1.
2. Henbest, H.B.; Wilson, R.A.L. *J. Chem. Soc.* **1957**, 1958.
3. Sharpless, K.B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, 95, 6136.
4. Katsuki, T.; Sharpless, K.B. *J. Am. Chem. Soc.* **1980**, 102, 5974.
5. (a) David Xu synthesized 4 and ent-4 in 1991 during his work on the AD mechanism, from which synthesis of 3 and ent-3 was implicit; two other groups reported this reaction sequence: (b) Corey, E.J.; Noe, M.C.; Shieh, W.C. *Tetrahedron Lett.* **1993**, 34, 5995–5998; (c) Vidari, G.; Dapiaggi, A.; Zaroni, G.; Garlaschelli, L. *Tetrahedron Lett.* **1993**, 34, 6485–6488; (d) Vidari, G.; Giori, A.; Dapiaggi, A.; Lanfranchi, G. *Tetrahedron Lett.* **1993**, 34, 6925–6928. Gerry Crispino's juvenile hormone iii synthesis demonstrates the same conversion: (e) Crispino, G.A.; Sharpless, K.B. *Synthesis* **1993**, 8, 777.
6. (a) Zhang, W.; Loebach, J.L.; Wilson, S.R.; Jacobsen, E.N. *J. Am. Chem. Soc.* **1990**, 112, 2801; (b) Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron Lett.* **1990**, 31, 7345.
7. (a) Knowles, W.S.; Sabacky, M.J. *J. Chem. Soc. Chem. Commun.* **1968**, 1445; (b) Dang, T.P.; Kagan, H.B. *J. Chem. Soc. Chem. Commun.* **1971**, 481 (c) Knowles, W.S.; Sabacky, M.J.; Vineyard, B.D.; WeinkauV, D.J. *J. Am. Chem. Soc.* **1975**, 97, 2567–2568. (d) See his excellent review: Halpern, J. *Science* **1982**, 217, 401. (e) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, 102, 7932–7934.
8. (a) Takaya, H.; Ohta, T. "Asymmetric Hydrogenation" In *Catalytic Asymmetric Synthesis*, Ojima, I. Ed.; VCH Publishers: New York, **1993**; pp. 1–39; (b) Kumobayashi, H.; Akutagawa, S.; Otsuka, S. *J. Am. Chem. Soc.* **1978**, 100, 3949; (c) Akutagawa, S.; Tani, K. "Asymmetric Isomerization of Allylamines" In *Catalytic Asymmetric Synthesis*; Ojima, I. Ed.; VCH Publishers, Inc.: New York, 1993; pp. 41–61. A history and review of the development of the asymmetric hydrogen migration of allylamines can be found in: (d) Otsuka, S.; Tani, K. *Synthesis* **1991**, 665–680.
9. For review chapters on both the AE and AD written largely by Roy Johnson despite being co-authored by both of us, see: (a) Johnson, R.A.; Sharpless, K.B. "Catalytic Asymmetric Epoxidation of Allylic Alcohols" In *Catalytic Asymmetric Synthesis*, Ojima, I. Ed.; VCH Publishers: New York, **1993**; pp. 101–158; (b) Johnson, R.A.; Sharpless, K.B. "Catalytic Asymmetric Dihydroxylation" In *Catalytic Asymmetric Synthesis*, Ojima, I. Ed.; VCH Publishers: New York, **1993**; pp. 227–272.
10. Jacobsen, E.N. "Asymmetric Catalytic Epoxidation of Unfunctionalized Olefins" In

- Catalytic Asymmetric Synthesis, Ojima, I. Ed.; VCH Publishers: New York, **1993**; pp. 159–202.
11. (a) Ko, S.Y.; Lee, A.W.M.; Masamune, S.; Reed, L.A.; Sharpless, K.B.; Walker, F.J. *Science* **1983**, 220, 949; (b) Ko, S.Y.; Lee, A.W.M.; Masamune, S.; Reed, L.A.; Sharpless, K.B.; Walker, F.J. *Tetrahedron* **1990**, 46, 245.
  12. (a) Sharpless, K.B. *CHEMTECH* **1985**, 692; (b) Sharpless, K.B. *Chem. Brit.* **1986**, 22, 1.
  13. M.G. Finn's thesis work has appeared in two full papers: (a) Woodard, S.S.; Finn, M.G.; Sharpless, K.B. *J. Am. Chem. Soc.* **1991**, 113, 106; (b) Finn, M.G.; Sharpless, K.B. *J. Am. Chem. Soc.* **1991**, 113, 113.
  14. (a) Criegee, R. *Justus Liebigs Ann. Chem.* **1936**, 522, 75; (b) Criegee, R. *Angew. Chem.* **1937**, 50, 153; (c) Criegee, R. *Angew. Chem.* **1938**, 51, 519; (d) Criegee, R.; Marchand, B.; Wannowias, H. *Justus Liebigs Ann. Chem.* **1942**, 550, 99.
  15. Sharpless, K.B.; Akashi, K. *J. Am. Chem. Soc.* **1976**, 98, 1986.
  16. van Rheenen, V.; Kelly, R.C.; Cha, P.Y. *Tetrahedron Lett.* **1976**, 1973.
  17. Hentges, S.G.; Sharpless, K.B. *J. Am. Chem. Soc.* **1980**, 102, 4263.
  18. (a) Cleare, M.J.; Hydes, P.C.; Griffith, W.P.; Wright, M.J. *J. Chem. Soc., Dalton Trans.* **1977**, 941; (b) Griffith, W.P.; Skapski, A.C.; Woode, K.A.; Wright, M.J. *Inorg. Chim. Acta* **1978**, 31, 1413.
  19. Five years later Bob Hanson made the simple but wonderful discovery that adding molecular sieves to the reaction dramatically increases catalyst turnover so that the AE process became truly catalytic: Hanson, R.M.; Sharpless, K.B. *J. Org. Chem.* **1986**, 51, 1922.
  20. Steve Pedersen provided invaluable structural results to aid M.G. Finn's studies during this period. Steve's work gave us our first glimpse into the dynamic world of complex mixtures in rapid equilibrium with each other. His contributions are summarized in: Sharpless, K.B. *Chemica Scripta (Sweden)* **1987**, 27, 521. These studies led to no new catalysts, but they drove home our appreciation for the absolute need for a ligand-acceleration effect in catalyst systems where ligand exchange is rapid.
  21. Kirshenbaum, K.S. Ph.D. Thesis, Massachusetts Institute of Technology, **1985**.
  22. Burns, C.J. Ph.D. Thesis, Massachusetts Institute of Technology, **1989**.
  23. Jacobsen, E.N.; Markó, E.I.; France, M.B.; Svendsen, J.S.; Sharpless, K.B. *J. Am. Chem. Soc.* **1989**, 111, 737.
  24. Jacobsen, E.N.; Markó, E.I.; Mungall, W.S.; Schröder, G.; Sharpless, K.B. *J. Am. Chem. Soc.* **1988**, 110, 1968.
  25. Shibata, T.; Gilheany, D.G.; Blackburn, B.K.; Sharpless, K.B. *Tetrahedron Lett.* **1990**, 31, 3817.
  26. Sharpless, K.B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lübber, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, 56, 4585.
  27. Sharpless, K.B.; Amberg, W.; Bennani, Y.; Crispino, G.; Hartung, J.; Jeong, K.; Kwong, H.L.; Morikawa, K.; Wang, Z.M.; Xu, D.; Zhang, X.L. *J. Org. Chem.* **1992**, 57, 2768.
  28. Crispino, G.; Jeong, K.S.; Kolb, H.; Wang, Z.M.; Xu, D.; Sharpless, K.B. *J. Org. Chem.* **1993**, 58, 1958.
  29. Wai, J.S.M.; Markó, I.; Svendsen, J.S.; Finn, M.G.; Jacobsen, E.N.; Sharpless, K.B. *J. Am. Chem. Soc.* **1989**, 111, 1123.
  30. Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem.* **1990**, 55, 766.
  31. Kwong, H.; Sorato, C.; Ogino, Y.; Chen, H.; Sharpless, K.B. *Tetrahedron Lett.* **1990**, 31, 2999.
  32. Private communication from Dr. Yun Gao, formerly with Sepracor, Inc., Marlborough, MA.
  33. Sharpless, K.B.; Teranishi, A.Y.; Bäckvall, J.E. *J. Am. Chem. Soc.* **1977**, 99, 3120.
  34. (a) Jacobsen, E.N.; Markó, E.I.; France, M.B.; Svendsen, J.S.; Sharpless, K.B. *J. Am. Chem. Soc.* **1989**, 111, 737; (b) Göbel, T.; Sharpless, K.B. *Angew. Chem., Int. Ed. Eng.* **1993**, 32, 1329; (c) Norrby, P.O.; Kolb, H.; Sharpless, K.B. *Organometallics*, **1994**, 13, 44; (d) Kolb, H.C.; Andersson, P.G.; Bennani, Y.L.; Crispino, G.A.; Jeong, K.S.; Kwong, H.L.; Sharpless, K.B. *J. Am. Chem. Soc.* **1993**, 115, 12226; (e) Kolb, H.C.; Andersen, P.G.;

- Sharpless, K.B. *J. Am. Chem. Soc.* **1994**, 116, 1278; (f) Kwong, H.L. Ph.D. Thesis, Massachusetts Institute of Technology, **1993**.
35. (a) Boar, R.B.; Damps, K. *Tetrahedron Lett.* **1974**, 3731; (b) Barton, D.H.R.; Jarman, T.R.; Watson, K.G.; Widdowson, D.A.; Boar, R.B.; Damps, K. *J. Chem. Soc., Chem. Commun.* **1974**, 861; (c) Barton, D.H.R.; Jarman, T.R.; Watson, K.G.; Widdowson, D.A.; Boar, R.B.; Damps, K. *J. Chem. Soc., Perkin I* **1975**, 1134.
36. Crispino, G.; Sharpless, K.B. *Tetrahedron Lett.* **1992**, 33, 4273.
37. Crispino, G.A.; Ho, P.T.; Sharpless, K.B. *Science* **1993**, 259, 64.
38. Hawkins, J.M.; Meyer, A. *Science* **1993**, 260, 1918.