Organic Synthesis

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# "Black Swan Events" in Organic Synthesis**

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These days one often hears the phrase "go viral" applied to a particular internet video that becomes extremely popular in a short period of time. I have been an avid reader of the chemical literature, especially that pertaining to organic synthesis, for 40 years now and have noticed that the same sort of spectacular event periodically occurs with areas of research. These occurrences seem to go hand in hand with changes in "conventional wisdom"—those underlying assumptions that color our thinking and influence the choice of experiments we are willing to undertake.

When conventional wisdom is correct, it is extraordinarily useful. One can imagine an unlimited number of experiments that one might attempt en route to a particular synthetic target. The choice needs to be informed based on the collective experience of the synthetic community.

But when conventional wisdom is wrong, things get really exciting. A paper overturning one such venerable assumption can spawn entirely new fields of research. The years that follow such a publication often see the appearance of hundreds or even thousands of publications extending and building upon the initial report. Given these powerful consequences, it seems very worthwhile to understand as much as we can about how such changes come about.

To provide a basis for this discussion, I will choose ten pieces of conventional wisdom that were widely accepted in 1976, the year I began my career in chemistry at DuPont Central Research, and trace their fate over the following 35 years. If you are a synthetic chemist and haven't been living under a rock for the last several years, you will likely be familiar with this chemistry. However, the details of how we reached our current understanding may surprise you.

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You will notice that the first five examples are discussed in greater detail than the five that follow. As explained later, this situation is a consequence of the existence of two distinct subsets of stories, which I refer to as "change through revolution" versus "change through evolution". Undoubtedly, these categories are somewhat arbitrary. The first category applies when a single paper instantly transforms a field and destroys the existing paradigm. The latter evolutionary model applies when no single contribution can undo the conventional wisdom; rather a "toolbox" of new methodology is required to complete the transformation. In my view, both types of change are equally essential for progress in the field.

Please note that the following ten examples are in no way intended to be comprehensive. They represent one chemist's altogether too fallible recollections. Even within the selected examples, I have without a doubt overlooked important contributions by a number of chemists. I apologize to them in advance for the unintentional oversight.

## Change through Revolution

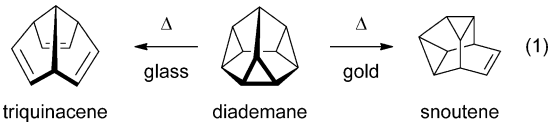
### 1. "Gold compounds are simply too unreactive to be useful as homogeneous catalysts"

This assumption was quite seductive because it seemed consistent with the well-known inertness of metallic gold. Indeed, the utility of this element in applications ranging from dental medicine to jewelry stems from the fact that it is not readily oxidized. In retrospect, such a conceptual leap from the lack of reactivity of elemental gold to the catalytic properties of gold complexes in solution is itself unwarranted. Nevertheless, as recently as 1995, a prominent review on gold chemistry summarized what had been the prevailing view in these words: "*The general doctrine appears to have been that gold, in contrast to its neighbor element on the periodic table, platinum, in neither the homogeneous nor the heterogeneous phase exhibits activity that is in any way satisfactory. Gold was considered to be 'catalytically dead'*".[1]

I completed my graduate studies with Prof. Jay Kochi at Indiana University in 1976. Although research for my thesis focused on organomercury chemistry, there was an active program on organogold chemistry, and our perspective was typical for its time. Gold was regarded as a lethargic and overweight version of catalytically interesting copper. Moreover, in the presence of water, gold(I) complexes have a nasty tendency to disproportionate to gold(III) and colloidal

gold(0).[2] Gold, it was thought, could provide insight into the workings of copper catalysis but was simply too inert to serve as a useful catalyst itself. Yet, during the decade after I completed my Ph.D. in 1976 there were tantalizing hints in the literature that this was not the case.

Interestingly, it was the perceived inertness of gold that led to the discovery of one of the earliest examples of homogeneous gold catalysis. When de Meijere and co-workers sought to study the thermal [2+2+2] cycloreversion of diademane to triquinacene [Eq. (1)], they constructed a flow system lined with metallic gold.[3] However, when diademane was passed through the gold-lined reactor at 100 °C, it was instead converted to snoutene. Subsequently, these researchers discovered that the same rearrangement could be catalyzed by a gold(I) complex, (dicyclopentadiene)AuCl, in solution at room temperature.




And there were other hints. The first example of a homogeneous gold-catalyzed oxidation reaction is generally regarded to be the 1983 report of Natile and co-workers[4] on the Au-catalyzed oxidation of sulfides to sulfoxides. However, analytical chemists in the gold-mining industry have long harnessed the ability of gold to catalyze the oxidation of certain organic dyes as a means of assaying ore samples.[5] At least one of these reports actually predates the Natile publication.[5a] Significantly, it could be shown that other precious metals do not catalyze the same reactions, the assays are specific for gold. It is safe to say that the synthetic community was not familiar with this report.

Figure 1 tracks the appearance of research publications on homogeneous gold catalysis during the period 1976–2010.[6] This tabulation differs from an earlier analysis[7] in that it focuses exclusively on homogeneous catalysis. The data have been manually vetted to eliminate duplication and false hits and exclude review articles and the "gray area" of catalysis that involves gold nanoparticles. The bottom line is that,

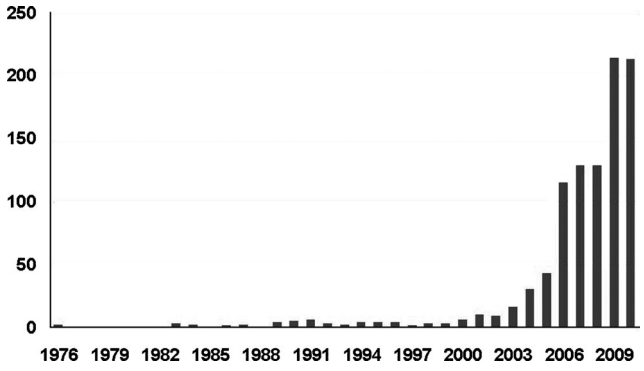
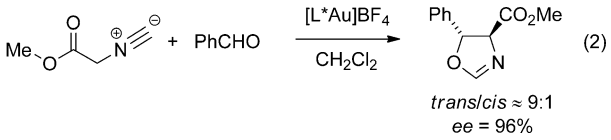



***Figure 1.*** Research publications on homogeneous gold catalysis by year.

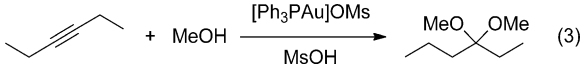
despite the pioneering results of de Meijere and a handful of earlier publications,[8] no sustained research effort in homogeneous gold catalysis would be undertaken until the mid-1980s.

The modest activity in the decade 1986–1995 largely grew from the gold-catalyzed asymmetric aldol reaction developed by Hayashi and co-workers.[9] This reaction involved the addition of an isocyanide to an aldehyde in the presence of a chiral cationic gold complex [Eq. (2)]. This transformation was an important contribution to organic synthesis and the first intermolecular[10] catalytic asymmetric aldol reaction of any sort. Nevertheless, the field of homogeneous gold catalysis did not immediately blossom; explosive growth was still several years in the future.




Why didn't fascinating new chemistry like that reported by de Meijere or Hayashi cause the catalysis community to question the conventional wisdom and start a broad exploration of gold catalysis? In both cases, it was easy to regard the results as "exceptions that prove the rule" rather than to recognize them as the first examples of a new paradigm. The de Meijere chemistry was specific to highly strained small rings. In Hayashi's chemistry, the role of gold could be rationalized as providing a Lewis acid site within a chiral array, viewed in that way, gold was simply a glorified main-group element. However, the next development was not so easily dismissed.

The ultimate spark for the explosive growth of homogeneous gold catalysis seems to be a 1998 publication by Teles and co-workers.[11] This group reported that a cationic gold(I) complex could catalyze the rapid addition of oxygen nucleophiles to acetylenes with turnover numbers that were orders of magnitude higher than those for previous catalysts. One example is shown in Equation (3). Two of the most prolific participants in the gold rush that followed noted the critical impact of the Teles publication. Toste asserted that he was "*initially attracted to the field of gold catalysis by the pioneering report of Teles and co-workers*".[12] Hashmi has called the paper "*a major breakthrough … probably in the whole field of gold catalysis*".[7]




It is noteworthy that Fukuda and Utimoto[13] had earlier reported the use of gold halide catalysts ($NaAuCl_4$) for the addition of nucleophiles to acetylenes. Such catalysts survived for only circa 50 turnovers before being deactivated by reduction to gold metal. One critical advance in the Teles paper is the use of a cationic gold complex that contains a less

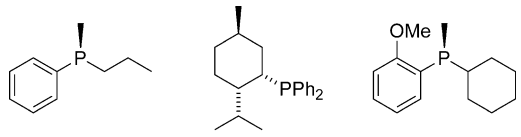
  

nucleophilic mesylate counterion.[14] This strategy, which continues to be widely utilized for many gold-catalyzed reactions, had previously been successful for catalysis using other transition metals (Rh, Cu, Pd).[15] Even more germane, Hayashi's aldol catalyst [Eq. (2)] was a cationic complex that contained a very non-nucleophilic tetrafluoroborate anion.

The explosion of research reflected in Figure 1 has begun to impact the field of organic synthesis. To date, homogeneous gold catalysis has been used in a growing number of natural product syntheses[16] and such applications seem certain to increase.

### 2. "*Efficient asymmetric hydrogenation will generally require the use of chelating (bidentate) ligands*"

Monodentate phosphane ligands were used in the earliest examples of asymmetric hydrogenation. In the 1968 publications of Knowles[17] and Horner,[18] the catalysts were modifications of Wilkinson's catalyst [$(Ph_3P)_3RhCl$], in which the triphenylphosphane ligands were replaced with chiral methylpropylphenylphosphane (MPPP, Scheme 1). The ee values in those early studies were modest (< 30 % ee),[19] but by 1971, Morrison[20] was reporting improved selectivity (up to 61 % ee in the reduction of β-methylcinnamic acid) using the neomenthyldiphenylphosphane (NMDPP, Scheme 1).




(*S*)-MPPP
Horner, Knowles
1968

NMDPP
Morrison
1971

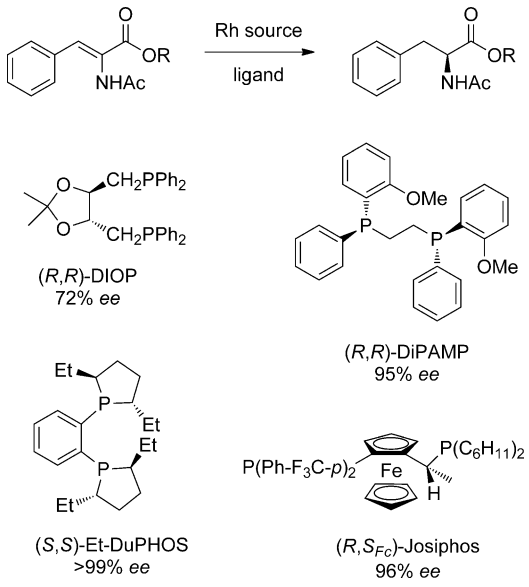
(*S*)-CAMP
Knowles
1972

***Scheme 1.*** Early examples of enantiomerically enriched monophosphane ligands.

It is ironic to note that, in the earliest days of homogeneous hydrogenation, it was actually believed that bidentate diphosphanes would be unsuitable as ligands. Mechanistic studies had shown that dissociation of a phosphane from Wilkinson's complex was essential for initiation of the catalytic cycle. It was assumed that the chelate effect of bidentate diphosphanes would interfere with this process.[21]

However, all this was about to change. By the time I completed my graduate studies in 1976, the catalysis community had essentially abandoned monodentate ligands in favor of chelating bidentate phosphanes. The use of monodentate phosphorus ligands in asymmetric hydrogenation would remain largely unexplored for the next 30 years.[22]

The perceived superiority of bidentate ligands first emerged in studies on the benchmark hydrogenation of acetamido cinnamic acid (Scheme 2). In 1971, Kagan disclosed the chelating diphosphane DIOP, which allowed this hydrogenation to be carried out in more than 70 % ee.[23] Knowles subsequently reported the use of DiPAMP, which increased the selectivity to 95 %.[24] Monsanto would utilize DiPAMP in the manufacture of L-DOPA (a drug for the




***Scheme 2.*** Rhodium-catalyzed asymmetric hydrogenation of acetamidocinnamates using bidentate phosphane ligands.

treatment of Parkinson's disease) in the first commercial application of asymmetric hydrogenation.[25]

The notion that bidentate ligands were required for efficient asymmetric hydrogenation grew from this relatively limited experience. The experimental results were rationalized in terms of the need for a structurally rigid catalyst architecture. As Dennis Riley, working at at Monsanto at the time, summarized the available information in 1980: "*From such studies, an important point has emerged; namely, those phosphines giving stereochemically more rigid complexes generally function as better (higher optical yields) chiral catalysts. For example, chiral bidentate phosphine ligands are better for generating chirality than monodentate phosphines…*"[26] From the vantage point of 2012, this language may seem somewhat dogmatic, but based on the extant evidence at the time, no referee was likely to question it.

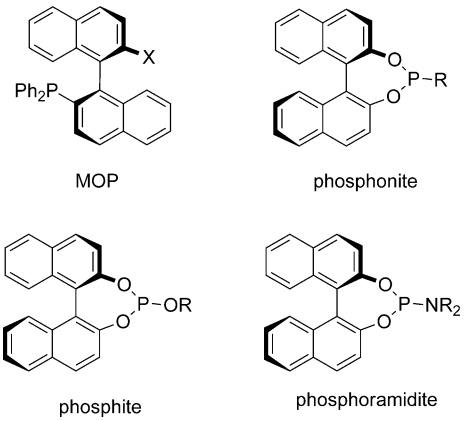
The use of bidentate ligands blossomed during the following decades, culminating in the introduction of the DuPHOS ligands[27] and a portfolio of ferrocene-containing ligands from Solvias, exemplified by Josiphos.[28] The structures of these ligands are shown in Scheme 2.[29] The use of monodentate ligands in asymmetric hydrogenation lay dormant for three decades, which is surprising for several reasons. To begin with, such simple ligands offered the potential advantage of simpler synthesis. Although the earliest ligands based on P-centered chirality required laborious resolution, by 1971 Morrison's simple preparation of NMDPP had shown that this did not need to be the case.[20]

Secondly, it can be noted that Monsanto came close to commercializing the L-DOPA process using a monodentate ligand. That ligand, CAMP (Scheme 1), promoted the benchmark hydrogenation (Scheme 2) in up to 88 % ee; the selectivity observed for DiPAMP was only marginally higher at 95 % ee.[24]

Thirdly, it became evident that monodentate ligands function extremely well for other catalytic enantioselective

reactions. Perhaps the most striking example is the development of the monodentate MOP ligands (Scheme 3) by Hayashi and co-workers.[30] MOP ligands were intended for




***Scheme 3.*** Families of chiral, monodentate phosphorus ligands.

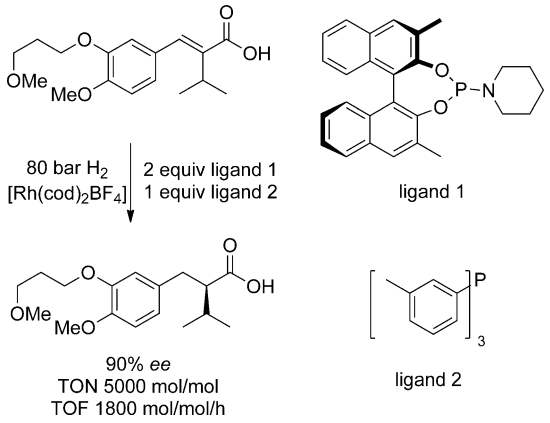
use in transformations in which a single ligand is bound to the catalytic metal during the catalytic cycle, and often provided ee values in the range of 90–95% in such cases. This ligand family was not intended for use in hydrogenation reactions in which the need for two tightly binding ligands was recognized. Nevertheless, their success brings into question whether chelation is necessary to achieve the structural rigidity required for high enantioselectivity.

The initial breakthrough involved not phosphanes but other phosphorus ligands. This in itself ran contrary to the prevailing mantra. The use of phosphanes (as opposed to, say, phosphites) reflected the belief that relatively electron-rich ligands were required for effective homogeneous hydrogenation. The argument was that oxidative addition of hydrogen, which is generally rate-limiting in such reactions, requires an electron-rich metal center to proceed at a practical rate. Only phosphanes were considered likely to provide the necessary electron density.

The year 2000 stands as a sort of "Wunderjahr" in this field. Three different research groups nearly simultaneously reported monodentate phosphorus ligands that could provide both high enantioselectivity and practical rates for asymmetric hydrogenation (Scheme 3).[31] In each case, the catalyst was a rhodium complex bearing two monodentate phosphorus ligands. Pringle, Claver, and co-workers described the use of biarylphosphonites,[32] Reetz and Mehler reported on monophosphite ligands,[33] while Feringa, de Vries, and co-workers utilized phosphoramidites.[34]

In particular, phosphoramidites have had a significant commercial impact. These ligands were developed as part of a collaboration between DSM Pharmaceutical Products and the University of Groningen,[35] and serendipity played a role in their discovery. Monodentate phosphoramidite ligands were originally developed by the Feringa group in the context of catalytic asymmetric conjugate addition reactions, and had proven spectacularly successful in that regard.[36] After use of chelating bis-phosphoramidites as ligands gave disappointing results in asymmetric hydrogenation, it was decided to look at their monodentate counterparts. When rhodium catalysts bearing such "MonoPhos" ligands were utilized, ee values in the 95–99% range were observed with reaction rates that in some cases rivaled those obtained with bis(diarylphosphanes).[37] A fascinating development is the independent discovery in both the Feringa and Reetz groups that a mixture of two different chiral monodentate ligands can in some cases perform better than either of the individual ligands.[38,39] In fact, a mixture of one chiral monodentate ligand and one achiral phosphane can also improve rates and/or selectivities.[40]

Work at DSM over the past several years has demonstrated that monodentate ligands can have powerful advantages for the rapid development of enantioselective hydrogenations for targets of commercial interest.[35] The MonoPhos ligands are easy to prepare, allowing their robotic parallel synthesis, a procedure that DSM refers to as an "instant ligand library". Moreover, the presence of two different ligands in the active catalyst naturally lends itself to a combinatorial strategy for catalyst optimization. A compelling example is the manufacture of the prescription sleep drug aliskiren (Scheme 4).[41] In this case, screening identified a rhodium catalyst bearing the phosphoramidite ligand 3,3′-dimethyl-PipPhos in combination with achiral tri-*m*-tolylphosphane as a highly efficient catalyst for manufacture of a key intermediate.




***Scheme 4.*** Manufacture of aliskiren intermediate by asymmetric hydrogenation.

Together with such experimental success has come new structural understanding. Yes, structural rigidity is critical, but cis coordination of two sterically demanding monodentate ligands can in some cases lead to highly stable structures with advantageous features for selective catalysis.[32] Moreover, the field has come full circle, and examples of efficient monodentate phosphane ligands for some types of asymmetric hydrogenation have begun to appear[42,43]

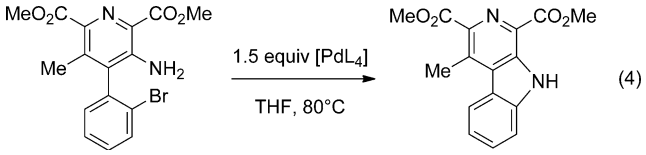
### *3. "Palladium-catalyzed cross-coupling is suitable for formation of C–C bonds but not for C–N bonds"*

By our benchmark year of 1976, the copper-promoted reaction of an aniline with an aryl halide to afford a diphenyl-

amine (the Jourdan–Ullmann–Goldberg reaction) had been known for 70 years[44] and was used on an industrial scale.[45] As practiced in that period, such reactions were characterized by harsh conditions and limited scope so there was ample reason to seek alternative catalysts. By that time, the ability of palladium to activate aryl halides had been demonstrated in the case of C–C bond forming reactions, such as the Heck olefination and Kumada coupling. Yet, one finds no indication in the literature of any attempt to utilize palladium catalysis for the synthesis of arylamines prior to 1983.

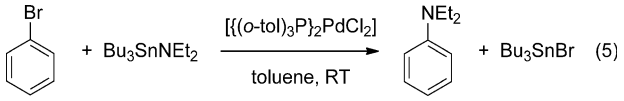
The success of Ullmann-type coupling indicated that the coupling of amines and aryl halides was thermodynamically allowed. As I attempt to reconstruct the thinking in 1976, I believe there was a general sense that palladium catalysis simply did not provide a kinetic pathway for such an amination. If so, this belief would have been reinforced by the report of Boger and Panek[46] regarding the palladium-promoted synthesis of the β-carboline ring needed for lavendamycin [Eq. (4)]. The reaction worked well when a stoichiometric amount of $[Pd(PPh_3)_4]$ was utilized; however, attempts to render the reaction catalytic were unsuccessful.




(4)

In 1983, Migita and co-workers published their pivotal paper on the palladium-catalyzed amination of aryl bromides with tin amides [Eq. (5)].[47] This reaction was modeled after the Stille reaction (cross-coupling of organotin reagents with aryl halides). Despite the unprecedented nature of this work, the Migita paper received little attention during the decade following its publication.[48]

However, by 1994, two research groups had recognized the significance of the Migita paper and were working to understand and extend its chemistry. In that year, Guram and

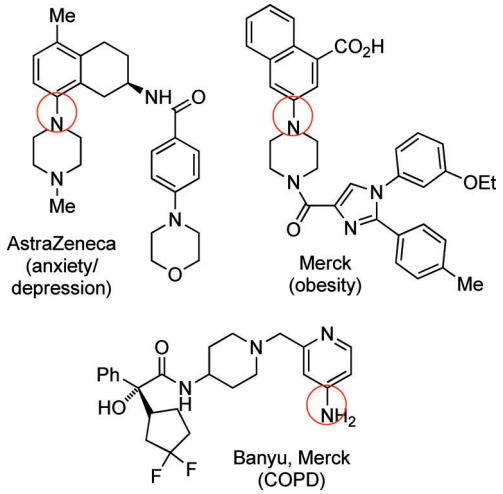



(5)

Buchwald[49] demonstrated that tin amides could be generated in situ and utilized in the Migita protocol, while Hartwig and co-workers published a pair of mechanistic studies[50] on Equation (5). Continued research over the next two years led to the first examples of tin-free Pd-catalyzed C–N cross-coupling.[51,52]

The profusion of publications that ensued from the publications of Buchwald and Hartwig and their co-workers (no doubt additionally fueled by the friendly rivalry between the groups) relied heavily on mechanistic insight. Early studies supported two key findings: 1) the active catalyst bears a single phosphane ligand, and 2) deprotonation of the coordinated amine must precede reductive elimination of the product. Consequently, the steric bulk of the phosphane and the choice of base are critical factors in such reactions. A more recent, unexpected twist in this evolving story is the discovery that use of a bidentate ligand can actually be advantageous for certain types of substrates.[53]

From my perspective as a pharmaceutical process chemist, the greatly improved access to arylamines as a result of this work has been a real boon. Drug candidates featuring arylamine functionality continue to proliferate. Each of the examples in Scheme 5 has been manufactured on a multi-




***Scheme 5.*** Recent drug candidates containing the arylamine structural motif. COPD = chronic obstructive pulminary disease.

kilogram scale using Pd-catalyzed C–N bond formation reactions (C–N bonds circled in red)[54] and indeed would have been quite difficult to make without this chemistry. In fact, the impact of this technology may run even deeper. Recently, four of my colleagues at Vertex Pharmaceuticals published a study[55] on the factors that influence what sorts of molecules medicinal chemists prepare. One fascinating conclusion is that new synthetic methods impact the types of structures that are prepared and screened in the pharmaceutical industry. Thus, it is not unreasonable to suggest that the very existence of these recent drug candidates is a result of the discovery of Pd-catalyzed C–N cross-coupling chemistry.

Interestingly, it appears the field has now come full circle. Increased interest in the preparation of arylamines as pharmaceutical intermediates fueled renewed interest in copper-catalyzed amination chemistry. Recent advances, particularly the introduction of diamine ligands, have markedly improved on the old brute-force Ullmann coupling.[56]

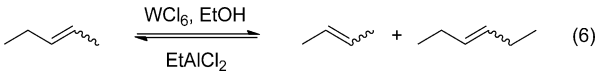
### *4. "Olefin metathesis is an ill-defined reaction of olefinic hydrocarbons and unlikely to find use in organic synthesis"*

Olefin metathesis was the child of the petrochemical industry. During the decade 1956–1965, the use of heterogeneous catalysts to promote this reaction was independently

discovered at Phillips Petroleum,[57] DuPont's Polychemicals Department,[58] and possibly at Standard Oil of Indiana as well.[59] The Phillips technology was actually used in the commercial conversion of propylene to ethylene and butenes as early as 1966.[60] However, most organic chemists were unaware of olefin metathesis prior to the publications of Calderon and co-workers at Goodyear beginning in 1967. These papers[61] were the first in the journal literature to describe olefin metathesis using a homogeneous catalyst.

The first paper in the series was unusual, to say the least. It contained no literature references whatsoever and reported the results of a single experiment—but what an experiment! It described the rapid disproportionation of 2-pentene [Eq. (6)] on a 0.1 mol scale using a catalyst prepared from tungsten hexachloride, ethanol, and ethylaluminum dichloride. At a 1000:1 substrate/catalyst ratio, "The mixture was allowed to stand for about one to three minutes at room temperature before being terminated with a drop of methanol."[61a]

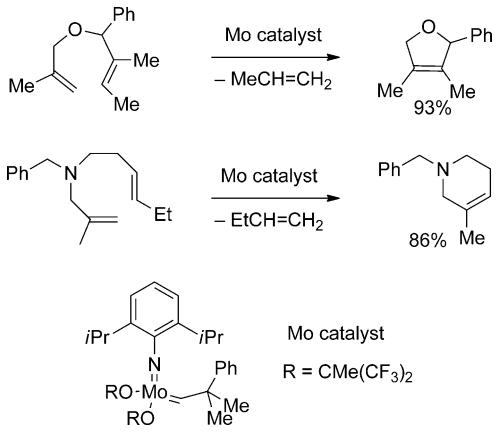



(6)

Despite the facility of this transformation, it was not rapidly adopted as a synthetic method. It is not difficult to see why. In this original embodiment, olefin metathesis was a procedure for turning one compound into a statistical mixture of three compounds, not typically a desired outcome in organic synthesis. The majority of applications during those early years involved non-functionalized hydrocarbons.[62,63] This partly reflected the rather ferocious Lewis acidic character of the catalyst system.[64] Beyond that, those early tungsten catalysts (as well as the molybdenum and titanium catalysts, which would later come into use) are highly oxophilic. Functional groups of interest to organic chemists would react with and destroy the catalyst. Even less reactive functional groups, such as esters, would bind to the active sites of the catalyst, thus limiting conversion.

It was exciting to observe the rapid progress in this field in the years that followed—truly what Grubbs would later call "An Organometallic Success Story".[65] The first critical step was the demonstration that the Chauvin mechanism was operant,[66] because this identified transition metal/alkylidene complexes as the active catalysts. Armed with this information, organometallic chemists were able to synthesize single component catalysts that functioned in the absence of Lewis acid additives.[67] This effort culminated in the synthesis of the molybdenum complex shown in Scheme 6 by Schrock and coworkers.[68] This catalyst exhibited remarkably high activity and could, for example, promote the ring-closing metathesis of sterically encumbered and electron-poor dienes.

In 1992, Fu and Grubbs published a pair of papers,[69] demonstrating that the Schrock molybdenum catalyst could be used to prepare five-, six-, and seven-membered monocyclic systems containing oxygen and nitrogen atoms (two examples in Scheme 6). As noted by Deiters and Martin in their 2004 review article,[70] it was this pair of papers that first

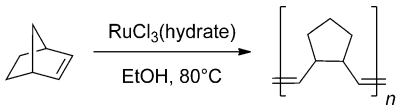



***Scheme 6.*** Ring-closing metathesis using the Schrock molybdenum catalyst.

alerted synthetic chemists to the exciting potential of ring-closing metathesis.

However, even this catalyst was not satisfactory for many synthetic applications. The affinity of molybdenum for the types of functionality utilized by synthetic chemists, that is, alcohols, aldehydes, amides, carboxylic acids and the like, was still too great.[71] There was a need for a catalyst that would react preferentially with alkenes in the presence of these other functional groups. The solution developed by Grubbs and co-workers was a series of catalysts based on a late transition metal, ruthenium. Once again, the literature provided a critical clue.

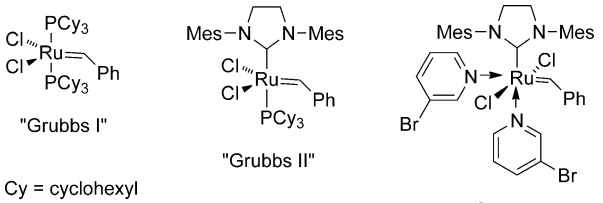
Back in 1965, two research groups[72] had found that a simple salt, ruthenium trichloride hydrate, would promote the ring-opening polymerization (ROMP) of norbornene derivatives [Eq. (7)], a reaction which proceeds through olefin metathesis. Grubbs and Novak reexamined the use of ruthenium salts to catalyze ROMP and found to their surprise that the reaction worked better when conducted in water, producing polymer of high molecular weight and low polydispersity.[73] Since evidence implicated the involvement of a ruthenium alkylidene complex, efforts then turned to the synthesis of such species.



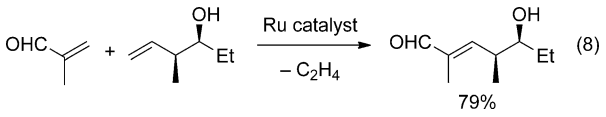

(7)

Ultimately, a series of such catalysts were prepared (Scheme 7).[74] All of these catalysts show excellent selectivity for olefins in the presence of other functionality; moreover, their activity has increased with each generation so that reaction rates now rival those obtained with early transition-metal catalysts.

Using these ruthenium catalysts, cross-metathesis has become an attractive route to highly functionalized alkenes, as exemplified in Equation (8).[75] For synthetic chemists of my generation, who were instilled with the conventional wisdom noted above, such transformations are frankly mind-boggling.




***Scheme 7.*** Three generations of Grubbs ruthenium-based olefin metathesis catalysts.

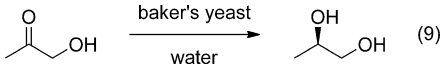



Such transformations open up entirely new pathways for organic synthesis. As one indication of the impact of ruthenium catalysis, Grubbs' 2001 Accounts article[65] has already been cited an astonishing 2500 times. However, the landscape may be changing yet again.

Recent improvements in tungsten and molybdenum catalysts have enabled some unprecedented achievements in olefin metathesis. These advances include enantioselective metathesis reactions[76] and most recently Z-selective cross-metathesis.[77] Especially exciting is progress in controlling the stereochemistry of macrocyclization reactions. Recently, a tungsten-based metathesis catalyst was used to achieve high Z selectivity in the synthesis of epothilone C and nakadomarin A.[78]

### 5. "Enzymatic reactions require water as solvent"

When a synthetic organic chemist ran an enzymatic reaction in 1976, it was likely to be a baker's yeast reduction, and it wasn't pretty. Such reactions were typically modeled on the procedure for the reduction of hydroxyacetone [Eq. (9)], described by Levene and Walti in Organic Syntheses.[79] Preparation of 50 grams of (*R*)-1,2-propanediol using this procedure required a slurry of 1 kilogram of yeast and 1 kilogram of sucrose in 10 liters of water. (Such reactions utilize whole cells rather than isolated enzymes, but serve to illustrate the difficulties inherent in the use of aqueous media.)




It was not difficult to convince oneself that water was essential for enzymes to function. Water was understood to play a critical role in key non-covalent interactions, maintaining enzymes in their native, catalytically active conformation. And yet, in what is becoming a familiar pattern, the literature contained hints that bulk water need not be present. In the mid-1960s, Dastoli and co-workers at Monsanto had disclosed that chymotrypsin[80] and xanthine oxidase[81] retained catalytic activity when suspended in organic solvents.

A citation search indicates that the Monsanto study attracted little attention. In his breakthrough publication in 1985, Alexander Klibanov could still observe, "*conventional wisdom dictates that water is required for enzyme action.*"[82] The absence of any follow-up during a period of 17 years is surprising, given the potential advantages of the approach. The original Klibanov paper provides what must now be regarded as a prophetic enumeration of those advantages: "*1) high solubility of most organic compounds in non-aqueous media; 2) ability to carry out new reactions impossible in water because of kinetic or thermodynamic restrictions; 3) greater stability of enzymes; 4) relative ease of product recovery from organic solvents as compared to water; and 5) the insolubility of enzymes in organic media, which permits their easy recovery and reuse and thus eliminates the need for immobilization.*"[82]

At the heart of this paradigm shift is the discovery that the catalytic activity of an enzyme in organic media depends on the pH value of the aqueous solution from which it is recovered, with maximum activity corresponding to the optimum pH value for activity in water. Because of this discovery, virtually any enzyme could be utilized in organic solvents. The further development of this field has resulted in some surprises regarding the effect of the solvent on regio- and stereoselectivity as well as many commercial applications. It is not an exaggeration to state that Klibanov's breakthrough has given rise to the establishment of an entire biocatalysis industry. The interested reader is referred to his review article.[83]

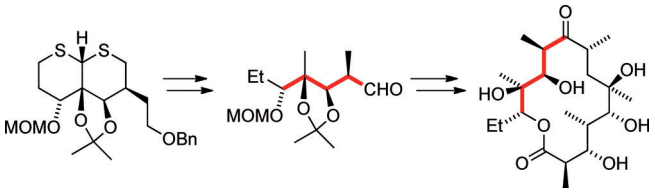
## Change through Evolution

### 6. "The combination of an acyclic electrophile and nucleophile is likely to lead to poor stereoselectivity"

This particular piece of conventional wisdom may sound somewhat esoteric, but at the time this belief had a profound impact on strategy for the synthesis of complex natural products. High stereoselectivity was thought to require structurally rigid intermediates. Rigidity was achieved by the temporary introduction of small (typically six-membered) rings into the synthetic sequence. A classic example is Corey's groundbreaking 1978 synthesis of erythronolide B in which a cyclohexane ring serves this function.[84]

Another impressive example is Woodward's synthesis of erythronolide A (Scheme 8).[85] In 1979, prior to the completion of that synthesis Woodward published an enlightening (and quite entertaining) essay,[86] in which he enumerated the underlying assumptions[87] in his synthetic approach to erythromycin: "*The armory of the synthetic chemist is richly endowed with weapons of great effectiveness in the stereoselective, or often stereospecific, generation of newly created asymmetric centers within rigid systems, as best exemplified by cyclic—and especially fused polycyclic—systems. By contrast, the construction of asymmetric arrays in a desired stereochemical sense in flexible, open-chain systems is rare, or little*

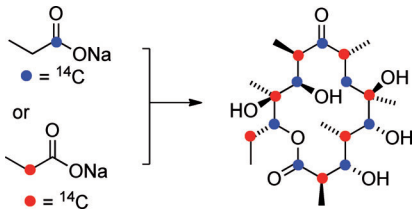


***Scheme 8.*** Woodward's approach to erythronolide A.

*understood when observed, and generalizations are dangerous.*"[86]

Woodward's solution was to utilize a rigid dithiodecalin ring as a template that not only provides structural rigidity but also enables a series of synthetic transformations during which the carbon skeleton is selectively "decorated" with the requisite substituents (Scheme 8). Ultimately, this sulfur scaffold is removed by treatment with Raney nickel. Woodward notes that this strategy represents "*the use of sulfur atoms to create rings by bridging carbon atoms that are destined to become methyl groups; indeed, a glamorization of the lowly, usually modest methyl group, which at first sight would hardly be expected to play a prominent role in the direction of stereoselective synthetic operations!*"[86]

This last phrase is particularly intriguing because Nature herself is demonstrably more impressed with the directing power of the "lowly" methyl group. In 1981, the very year in which the Woodward synthesis of erythronolide A appeared, Cane and co-workers reported the first in a series[88] of elegant labeling studies on the biosynthesis of this macrolide antibiotic (Scheme 9). These studies established that the complex skeleton of erythronolide A was assembled using simple propionate building blocks as the sole source of carbon atoms.

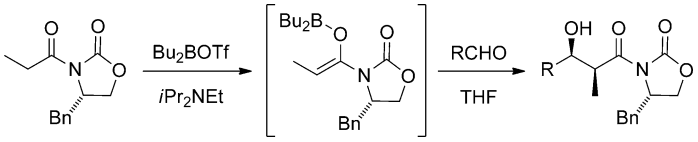


***Scheme 9.*** Isotopic labeling studies demonstrate the propionate origin of erythronolide A.

The effort to close the gap between the tools of organic synthesis and the high bar set by Nature is arguably the principal underlying theme of organic chemistry during the past three decades. This effort has included the development of asymmetric enolate alkylations, aldol reactions of chiral enolates and related Michael reactions, as well as nucleophilic additions to chiral aldehydes with major contributions from the laboratories of Ireland, Heathcock, Masamune, Evans, and many others.[89] These technologies are often lumped together under the heading "acyclic stereoselection", a term introduced[90] by Heathcock in 1977. (However, as noted in a recent review article,[91] many of these advances fall outside the strict definition of the term.)

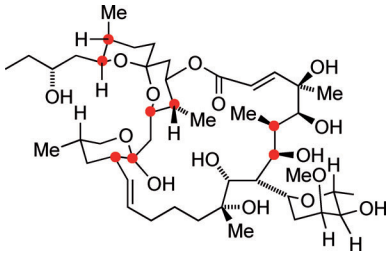
In this and the other "evolutionary" examples, it is simply not possible to record all the individual advances that together ultimately overturned conventional thinking. However, by way of illustration, let me choose one such contribution to highlight.

Particularly relevant to the preparation of erythronolide A and other polyketide antibiotics was the development of the "Evans aldol" reaction, which employs an oxazolidinone as a chiral auxiliary. For the case of propionate derivatives, this is exemplified in Scheme 10.[92] A critical feature of this transformation is the conversion of the N-acyloxazolidinone substrate to a dialkylboron enolate. These are formed under mild conditions[93] and the exceptionally short B–O distance apparently contributes to the high stereoselectivity of the process.[94]



***Scheme 10.*** The Evans aldol reaction as applied to propionate derivatives.

Evans and his co-workers demonstrated the utility of this transformation in the synthesis of several polyketides. I would in particular draw attention to his remarkable synthesis of the macrolide antibiotic cytovaricin (Scheme 11).[95] In this case, oxazolidinone aldol methodology was used to install eight stereogenic centers (indicated in red). With such chemistry, organic synthesis has begun to approach Nature's adeptness in manipulating propionate fragments.



***Scheme 11.*** Structure of cytovaricin. Stereocenters indicated in red were installed using the Evans aldol reaction.

### *7. "Free radicals are high-energy intermediates, the chemistry of which is not sufficiently selective for C–C bond formation in organic synthesis"*

The evolutionary process was already underway[96] when Hart published his seminal paper in Science in 1984.[97] However, I believe (and a citation search supports this belief) that this call to arms galvanized the organic synthesis community and greatly stimulated subsequent advances. Today, free radical reactions are an integral part of the

synthetic chemist's armamentarium, as attested by a growing number of books devoted to the subject.[98]

#### 8. "Water is not a suitable solvent for organometallic chemistry"

This is another case in which industrial practice significantly predated academic interest. Kuntz introduced sulfonated phosphine ligands in 1976 and they were almost immediately applied in Rhône-Poulenc's high tonnage biphasic hydroformylation.[99] Over time, it has become evident that aqueous-phase organometallic chemistry is not only possible, but in many cases advantageous. As in the previous example, interest has blossomed to the extent that such reactions are the topic of entire books.[100]

#### 9. "Nucleophilic organometallic species, such as Grignard reagents, are incompatible with electrophilic substituents, such as esters and nitriles"

The watershed change in this perception has required an entire catalogue of new methodologies, many of which have emerged from the Knochel and Snieckus laboratories. Key contributions have included improved protocols for halogen–metal exchange, in particular the promoting effect of lithium halides,[101] advances in organozinc chemistry,[102] and directed ortho- and remote-metalation chemistry.[103] Remarkably, even nitroarenes, despite their pronounced tendency toward redox chemistry, can nowadays be converted to useful organometallic reagents.[104]

#### 10. Efficient (non-enzymatic) enantioselective catalysis requires the use of a metal complex

Asymmetric transition-metal catalysis is usually dated to Nozaki's 1966 mechanistic study probing a copper-catalyzed carbene reaction.[105] It is noteworthy that the initial reports of highly enantioselective organocatalysis began to appear just a few years later with the independent discovery of proline-catalyzed intramolecular aldol reactions at Schering AG and at Hoffmann-La Roche in the early 1970s.[10,106] However, that five-year head start heavily influenced thinking; as one reviewer put it, "*Asymmetric catalysis has become almost synonymous with the use of metals in a chiral environment.*"[107] Nevertheless, the field of organocatalysis has seen explosive growth, beginning around the year 2000 with major contributions from the laboratories of List, Barbas, MacMillan, and others. Even among the ten areas of vigorous research highlighted in this Essay, this field has been an especially rich source of new subdisciplines. Examples include organocatalytic cyclization reactions,[108] peptide-catalyzed asymmetric synthesis,[109] and asymmetric phase-transfer catalysis.[110]

## Some Observations

The ten examples enumerated herein represent some of the most active fields of chemical research of today. In some cases they have spawned entire industries.

A common feature of these stories is that the literature invariably contains earlier hints that the conventional wisdom was not correct. This is particularly easy to see in the revolutionary examples, because one can assign a date to the change in question. I refer to these antecedents as "Black Swan events" (Table 1) for reasons that will become evident. It is clear from this tabulation that such hints were more or less ignored by the organic synthesis community for one, two, or even three decades after their publication.

In all cases, the authors of the breakthrough papers were aware of and indeed cited the antecedent publications. In examples (3) and (4), the breakthrough studies actually began with attempts to understand and extend the antecedent research.

I believe that the literature likewise foreshadows evolutionary changes in conventional wisdom. It is somewhat harder to establish the timeframe because the change occurs over an extended period. To cite an extreme example, Emil Fischer reported[111] the diastereoselective addition of potassium cyanide to D-(+)-mannose in 1889, some 88 years before Heathcock[90] coined the term "acyclic stereoselection". More typical examples are the early industrial applications of aqueous-phase organometallic catalysis or the early reports

*Table 1:* Literature antecedents for examples (1)–(5).

| Disruptive Breakthrough | "Black Swan Events" |
|---|---|
| Highly efficient catalytic activation of acetylenes with a cationic gold complex. **1998** | Catalytic activation of acetylenes using gold halides. **1991**<br>Use of a cationic gold catalyst in the asymmetric aldol reaction. **1986** |
| Practical monodentate phosphorus ligands for asymmetric hydrogenation. **2000** | Selective asymmetric hydrogenation of acetamidocinnamic acid derivatives with CAMP ligand. **1972**<br>Highly enantioselective hydrosilylation of olefins catalyzed with monodentate MOP ligand. **1991** |
| Palladium-catalyzed cross coupling of amines with aryl halides. **1995** | Palladium-catalyzed cross coupling of organotin amides with aryl halides. **1983** |
| Metathesis of functional olefins using ruthenium alkylidene catalyst. **1995** | $RuCl_3$-catalyzed ring-opening polymerization. **1965** |
| Use of enzymes in organic solvents as a potential synthetic tool. **1985** | Mechanistic studies demonstrate enzymatic catalysis in organic solvents. **1966** |

on the proline-catalyzed asymmetric aldol reactions that were published by pharmaceutical companies.

It is noteworthy that these last two pairs of antecedents from the evolutionary realm represent contributions from industry. This appears to be part of a larger pattern. Industrial contributions are also heavily represented in the revolutionary examples of Table 1. The literature antecedents for examples (2), (4), and (5) include publications from industrial laboratories. (In fact, the breakthrough research on homogeneous gold catalysis was done at BASF.) Moreover, we have previously noted that manufacturing plants utilizing olefin metathesis and aqueous-phase organometallic catalysis were already producing multi-ton quantities of material before most academic chemists were aware that the technology existed. As Knowles observed, "*In science, one can often use a phenomenon before one understands it.*"[25]

We are fortunate that the industrial chemists involved in these examples were able to publish their work, though in some cases after extended delays. I can tell you from years of experience that intellectual property lawyers are a wary lot who prefer to err on the side of caution. When carrying out a literature search, one ignores the patent literature at one's own peril. In some cases it can provide a treasure trove of interesting chemistry that has never appeared in the journal literature.

Regrettably, exploratory research in the chemical industry has become much less common in recent years. I am most familiar with the situation at DuPont Central Research, and there the change was premeditated. In 1999, the company abandoned the "technology-driven" model, which had given the world KTP frequency doubling, the nickel-catalyzed hydrocyanation of butadiene, non-ozone depleting refrigerants, and so many other major contributions.[112] That approach was replaced with the "Apex" program, which is based on "market pull" and addresses specific business opportunities. I understand the new model has achieved some success but nevertheless regret the passing of the old Central Research with its marvelous scientific freedom.[113]

Given the tremendous importance of the scientific advances in Table 1, why was there such a long interval between the literature clues and the breakthroughs? Part of the answer may relate to where these antecedents were published. Precious few synthetic organic chemists would have been leafing through the Archives of Biochemistry and Biophysics in 1966 to spot Monsanto's studies on enzymes in organic solvents. And would Migita's seminal demonstration of palladium-catalyzed C–N bond formation have been largely overlooked for over a decade if it had graced the pages of Angewandte Chemie or the Journal of the American Chemical Society? Clearly, it is important that potentially high-impact papers be published in high-impact journals.[114]

The situation is even more complicated in the case of olefin metathesis, in which the literature antecedents came from the polyolefin field. Again, the journals involved were not on the synthetic chemist's reading list but, beyond that, it was not recognized at the time that what we now call ring-opening metathesis polymerization and olefin metathesis involved the same reaction mechanism. The organic synthesis community should be eternally grateful that Grubbs' research interests straddled the fields of olefin polymerization and organic synthesis. Otherwise, I suspect that ruthenium-catalyzed olefin metathesis as a tool for organic synthesis would still lay undiscovered.

In some cases, it seems reasonable to argue that the field simply wasn't ready for change when the antecedent papers were published. For example, few purified enzymes of interest to synthetic chemists were available in 1965. Similarly, the concept of "green chemistry" had not yet been enunciated when Rhône-Poulenc and Montedison initially harnessed aqueous-phase organometallic catalysis in 1976. One gets the impression that an area must somehow be "ripe for change" in order for conventional wisdom to be overturned. Consistent with this perception are cases in which two or more research groups simultaneously publish breakthough results after years of inactivity. We have seen this effect in the area of palladium-catalyzed C–N bond formation and the use of monodentate ligands for asymmetric hydrogenation.

Could it be that human beings are hardwired to rationalize experimental results that conflict with our comfortable conceptual frameworks? Such a model, the "Black Swan Theory", has actually been proposed and I want to say a few words about this.

The phrase "Black Swan event" comes from the writings of the statistician and philosopher Nassim Nicholas Taleb.[115] The term derives from a Latin metaphor that for many centuries simply meant something that does not exist. But also implicit in the phrase is the vulnerability of any system of thought to conflicting data. The phrase's underlying logic could be undone by the observation of a single black swan.

In 1697, the Dutch explorer Willem de Vlamingh discovered black swans on the Swan River in Western Australia. Not surprisingly, the phrase underwent a metamorphosis and came to mean a perceived impossibility that might later be disproven. It is in this sense that Taleb employs it. In his view: "*What we call here a Black Swan (and capitalize it) is an event with the following three attributes. First, it is an outlier, as it lies outside the realm of regular expectations, because nothing in the past can convincingly point to its possibility. Second, it carries an extreme impact. Third, in spite of its outlier status, human nature makes us concoct an explanation for its occurrence after the fact, making it explainable and predictable.*"[115]

Taleb has documented this last point about human nature through historical and psychological evidence. His ideas remain controversial but seem to make a great deal of sense when one attempts to understand the lengthy interludes between the literature antecedents and the disruptive breakthroughs shown in Table 1. At the very least, his ideas represent a heads up as to how we read and mentally process the chemical literature.

I have no doubt that unwarranted assumptions persist in the conventional wisdom of organic synthesis. (Indeed, to believe otherwise would suggest that disruptive breakthroughs will no longer occur in the future.) The goal, it would seem, is to recognize such assumptions for what they are and to minimize the time lag between the appearance of Black Swans and the breakthroughs that follow.

In the absence of experimental evidence, conventional wisdom is just another working hypothesis. It represents a necessary step in the scientific method but should never be confused with natural law. Ultimately, the fact that something has never been done is the flimsiest of evidence that it cannot be done.

I hope that you found these observations thought-provoking. It seems to me, beyond serving as "food for thought" this discussion raises three "actionable" items which I will mention in closing.

First, there seems to be a disconnection between the continuing need for novel chemistry in industry and its abandonment of exploratory chemical research. More than ever, industry will depend on academia as a source of new direction. Given this situation, we in industry must find additional ways to support chemical research in the universities through the creative use of collaborations, financial support, and advocacy with government agencies who fund university research.

Secondly, if Taleb is correct regarding our human shortcomings in dealing with Black Swans, it will pay to be cognizant of this situation when reading the literature. When we spot a result that runs contrary to our chemical beliefs, before we attempt to rationalize and explain away such an outlier, it seems worthwhile to consider whether our underlying assumptions are adequately supported by experimental evidence.

The third and final point I will direct toward younger scientists. On a couple of occasions, I have encountered chemists who feel overwhelmed by the sheer volume of the current chemical literature. They report that they approach the literature in a reactive fashion—they utilize search engines like SciFinder or Beilstein to address specific research problems to the exclusion of browsing current journals. I strongly disagree with this approach.

It is by systematically reading current publications that we become aware of deficiencies in existing technologies, innovative solutions, research trends, and results from entirely different fields that could potentially impact our own interests. But I hope it is evident from the examples we have discussed that reading the literature over the last 40 years has been something more. It has, quite frankly, been an adventure. In such history one finds overarching themes, tales of dogged persistence, brilliant flashes of insight, and remarkable plot twists. One can only imagine what extraordinary developments those of you currently beginning your careers in chemistry will witness in the next 35 or 40 years. In this regard, I envy you.

Please note: Minor changes have been made to this manuscript since its publication in *Angewandte Chemie* Early View. The Editor.

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[1] "Nach allgemeiner Lehrmeinung schien Gold im Gegensatz zu seinem Nachbarelement im Periodensystem, dem Platin, weder in homogener, noch in heterogener Phase eine ausreichende, wie auch immer geartete, katalytische Aktivitaet aufzuweisen. Gold galt als 'katalytisch tot'". H. Schmidbaur, *Naturwiss. Rundsch.* **1995**, *48*, 443 – 451.

[2] One consequence was that the glassware cleaning tanks often turned a dark red–violet color, which is characteristic of colloidal gold.

[3] L.-U. Meyer, A. de Meijere, *Tetrahedron Lett.* **1976**, *17*, 497 – 500.

[4] F. Gasparrini, D. Giovannoli, D. Misiti, G. Natile, G. Palmieri, *Tetrahedron* **1983**, *39*, 3181 – 3184.

[5] a) A. Navas, F. Sanchez Rojas, *Quim. Anal.* **1983**, *2*, 112 – 122; b) O. A. Bilenko, S. P. Mushtakova, *Zh. Anal. Khim.* **1986**, *41*, 65 – 68; c) L. K. Shpigun, P. M. Kamilova, *J. Anal. Chem.* **2002**, *57*, 1049 – 1054.

[6] The complete database and a discussion of its construction is included as Supporting Information.

[7] A. S. K. Hashmi, *Gold Bull.* **2004**, *37*, 51 – 65.

[8] a) W. Schemberger, W. Gordon, *Chem. Zentralbl.* **1935**, *106*, 514 – 514; b) P. G. Gassman, G. R. Meyer, F. J. Williams, *J. Am. Chem. Soc.* **1972**, *94*, 7741 – 7748.

[9] Y. Ito, M. Sawamura, T. Hayashi, *J. Am. Chem. Soc.* **1986**, *108*, 6405 – 6406.

[10] The proline-catalyzed cyclic ketone synthesis of Hajos and Parrish represents an earlier example of an organocatalytic intramolecular aldol reaction: a) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem.* **1971**, *83*, 492 – 493; *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496 – 497; b) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615 – 1621.

[11] J. H. Teles, S. Brode, M. Chabanas, *Angew. Chem.* **1998**, *110*, 1475 – 1478; *Angew. Chem. Int. Ed.* **1998**, *37*, 1415 – 1418.

[12] N. D. Shapiro, F. D. Toste, *Synlett* **2010**, 675 – 691.

[13] a) Y. Fukuda, J. Utimoto, *J. Org. Chem.* **1991**, *56*, 3729 – 3731; b) Y. Fukuda, J. Utimoto, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2013 – 2015.

[14] See, for example: a) rhodium: R. R. Schrock, J. A. Osborn, *J. Am. Chem. Soc.* **1976**, *98*, 2134 – 2143; b) copper: J. T. M. Evers, A. Mackor, *Tetrahedron Lett.* **1978**, *19*, 2321 – 2324; c) palladium: G. Oehme, H. Pracejus, *Tetrahedron Lett.* **1979**, *20*, 343 – 344.

[15] When I shared an early version of this manuscript with Prof. Toste, he noted that the use of a simple, tunable phosphine in Teles's work likely contributed to its impact. In contrast, the Hayashi catalyst utilized a specialized phosphine, which at the time was not commercially available. "*In my opinion it was this 'perfect storm' of conceptually new reactivity (for example generation of gold carbenoids) but easily defined (alkyne activation), practically simple chemistry (stable precursors with commonly available ligands) using an unexplored transition metal that played a key role.*".

[16] As a sample of the range of such applications, see: a) (−)-rhazinilam: Z. Liu, A. S. Wasmuth, S. G. Nelson, *J. Am. Chem. Soc.* **2006**, *128*, 10352 – 10353; b) various terpenes: A. Fürstner, P. Hannen, *Chem. Eur. J.* **2006**, *12*, 3006 – 3019; c) ionomycin calcium complex: Z. Gao, Y. Li, J. P. Cooksey, T. N. Snaddon, S. Schunk, E. M. E. Viseux, *Angew. Chem.* **2009**, *121*, 5122 – 5125; *Angew. Chem. Int. Ed.* **2009**, *48*, 5022 – 5055; d) swainsonine: R. W. Bates, M. R. Dewey, *Org. Lett.* **2009**, *11*, 3706 – 3708; e) mersicarpene: R. Nakajima, T. Ogino, S. Yokoshima, T. Fukuyama, *J. Am. Chem. Soc.* **2010**, *132*, 1236 – 1237; f) angustureine: P. Kothandaraman, S. J. Foo, P. W. H. Chan, *J. Org. Chem.* **2009**, *74*, 5947 – 5952.

[17] W. S. Knowles, M. J. Sabacky, *Chem. Commun.* **1968**, 1445 – 1446.

[18] L. Horner, H. Siegel, H. Buethe, *Angew. Chem.* **1968**, *80*, 1034; *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 942.

[19] A complication in these early studies is that the ligands themselves were not optically pure. For example, the (−)-MPPP used in Ref. [17] was reported to have an ee value of

  

69%. It is not clear how great an impact this had on enantioselectivity, because the extent of chiral amplification for this catalyst is unknown.
[20] J. D. Morrison, R. E. Burnett, A. M. Aguiar, C. J. Morrow, C. Phillips, *J. Am. Chem. Soc.* **1971**, *93*, 1301 – 1303.
[21] For an enlightening discussion of the problems initially encountered with the use of diphosphane ligands in homogeneous catalysis, see: P. W. N. M. van Leeuwen, P. C. J. Kamer, J. N. H. Reek, P. Dierkes, *Chem. Rev.* **2000**, *100*, 2741 – 2770.
[22] It must be noted that studies using monodentate ligands for asymmetric hydrogenation did not completely cease. In general, exceptions represented cases, in which researchers briefly examined monodentate subunits that were later incorporated into bidentate ligands. However, catalysts prepared from two ligands, although sluggish, allowed the enantioselective hydrogenation of cinnamates with ee values of 92 and 87%, respectively: a) S. Saito, Y. Nakamura, Y. Morita, *Chem. Pharm. Bull.* **1985**, *33*, 5284; b) O. Riant, O. Samuel, T. Flessner, S. Taudien, H. B. Kagan, *J. Org. Chem.* **1997**, *62*, 6733.
[23] H. B. Kagan, T.-P. Dang, *J. Am. Chem. Soc.* **1972**, *94*, 6429 – 6433.
[24] B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, O. J. Weinkauff, *J. Am. Chem. Soc.* **1977**, *99*, 5946 – 5952.
[25] W. S. Knowles, *Acc. Chem. Res.* **1983**, *16*, 106 – 112.
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[27] a) M. J. Burk, *J. Am. Chem. Soc.* **1991**, *113*, 8518 – 8519; b) M. J. Burk, J. E. Feaster, W. A. Nugent, R. L. Harlow, *J. Am. Chem. Soc.* **1993**, *115*, 10125 – 10138.
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[112] Since our topic is organic synthesis, I note that much synthetic methodology had its origins at DuPont Central Research, including the Simmons–Smith reagent, the Tebbe reagent, the DAST fluorinating agent, titanocene monochloride, and the use of crown ethers in synthetic applications; a) H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1959**, *81*, 4256–4264; b) F. N. Tebbe, G. W. Parshall, G. W. Reddy, *J. Am. Chem. Soc.* **1978**, *100*, 3611–3613; c) W. J. Middleton, *J. Org. Chem.* **1975**, *40*, 574–578; d) T.-V. RajanBabu, W. A. Nugent, *J. Am. Chem. Soc.* **1994**, *116*, 986–997; e) Nobel lecture: C. J. Pedersen, *Angew. Chem.* **1988**, *100*, 1053–1059; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1021–1027.

[113] In 2011, for the first time in its 55 year history, no publication from DuPont Central Research appeared in *J. Am. Chem. Soc.* In its heyday as an engine of exploratory chemistry, the department was generating more than 60 such papers per year. For an analysis of the changing role of exploratory chemistry in industry based on publication records, see the Supporting Information.

[114] An often-cited example is Makosza's seminal publication reporting the first instances of phase-transfer catalysis, which appeared in a Polish language journal and was initially inaccessible to most synthetic chemists: T. Urbanski, B. Serafinawa, C. Belzecki, J. Lange, H. Marukawa, M. Makosza, *Rocz. Chem.* **1965**, *39*, 1595–1601.

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