Dedicated to Professor Gilbert Stork in celebration of 35 years in research and teaching.
About Our Cover:

When we asked our chemist-collector to allow us to reproduce his finest recent acquisition in the Acta dedicated to Professor Stork, he pointed to the painting (oil on panel, 23 1/2 x 17 1/2 inches) reproduced on our cover. "Not another Jacob's Dream!"

Our first reaction subsided quickly when we saw the quality of the painting — truly a dream in every sense of the word.

When it came up for sale in April of 1980, it was so covered by layers of dirty varnish (Fig. 1) that Christie's in London, who operate two auction galleries — one on King Street for better works and the other in Kensington for minor works — put it into the Kensington sale. It was attributed to one of the Carraccis, an artist family in Bologna early in the 17th century. Cleaning revealed that the painting is in excellent condition and is by Domenico Fetti, an artist who also worked early in that century in Rome, Mantua and Venice. Fetti often produced several versions of his compositions, and his best-known of this subject (Fig. 2) is in Vienna.

The painting had been sent to Christie’s by its former owner in Weymouth, Dorset, who had inherited it from his grandfather. Nothing is known of its previous history, although it must have belonged to a collector whose seal (Fig. 3) is burnt three times into the back of the panel. Our collector has not yet determined the identity of the seal, and we would be most grateful for help from any reader who recognizes it.

We are reminded of what we have written about this wonderful subject, in Vol. 8, No. 4 and Vol. 12, No. 3, of the Acta: "The Bible is the book of dreams, par excellence: dreams of individuals, dreams of a people, dreams of all mankind. It is surely no accident that the very first well known dream in the Bible is not that of a king or of a general but of a man at the lowest point in his life — homeless and hunted, yearning for God's promise that He would return him to his country.

"The vision of a ladder with angels going up and down on it is unique in Biblical imagery, and so Jacob's Dream has aroused artists' imaginations for centuries."

It seems a particularly fitting subject for the cover of this Acta, because Professor Stork — like Jacob — escaped from his homeland. We, in America, are lucky that Professor Stork did not return to France, but stayed with us and became one of our greatest chemists and teachers.

©1982 by Aldrich Chemical Company, Inc.
The Aldrich Sure/Seal™ system of packaging sensitive reagents is so effective that we wanted to use it on our own samples. We saved the bottles, obtained a set of teflon septa and steel crown caps, Aldrich Cat. Nos. Z10,215-6 and Z10,214-8, and then discovered that there was no way of applying a cap to a bottle without using a capping device, available, for example, from Sears. Since it was not immediately apparent in our laboratory that such devices are available, we’d like to share this knowledge with other chemists to facilitate their use of this excellent system.

Jeanne Hofsteezer  Marvin J. Hoard
Warner Lambert Co.
Pharmaceutical Research Division
Ann Arbor, MI 48105

Editor’s note:
Aldrich now offers the following capping devices:

In trace-level analytical methods, it is necessary to minimize background levels. When quenching fluorinated acid anhydride derivatization reactions using aqueous phosphate buffer solutions, we have found that pre-extracting the buffer with a suitable immiscible solvent, e.g., benzene, removes residues that could interfere with subsequent electron-capture gas-chromatographic assays. Also, the traces of benzene that remain in the buffer solution prevent the growth of mold. This treatment can also be applied to deionized water and NaOH solutions (inhibits carbonate formation) not only to minimize background, but to enhance stability on storage.

Charles Nony
Division of Chemistry
National Center for Toxicological Research
Jefferson, AR 72079

Preparation of dilute polymer solutions in 100-ml volumetric flasks is a routine task in our lab and wet resin invariably forms lumps, sometimes sticking to the wall of the flask.

While the use of a tiny magnetic stirring bar is common practice, we have found that its efficiency is notably increased when the flask is placed on its side. With the flask in this position the speed of mixing can be increased greatly without having the bar fly all over the flask. The vortex is deep and smooth. Finally, the liquid moves vigorously through the neck of the flask where stray resin often adheres.

When a large number of samples are involved this technique can speed up the entire process appreciably.

H. Russell Flanagan
Vice President,
Research and Development
Ruskai, Inc.
P.O. Box 43
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Any interesting shortcut or laboratory hint you’d like to share with Acta readers? Send it to Aldrich (attn: Lab Notes) and if we publish it, you will receive a handsome Aldrich coffee mug as well as a copy of Selections from the Bader Collection. We reserve the right to retain all entries for consideration for future publication.

"Please Bother Us."

Last December Dr. John Frost at Harvard suggested that solid tetrabutylammonium fluoride trihydrate would be even more useful than the THF solution we have been selling, simply because a solid is so much more convenient to handle. The solution can corrode syringes, and sometimes solvents other than THF are needed. We had thought that the solution would be more convenient, but of course we are happy to offer the solid also.

It was no bother at all, just a pleasure to be able to help.
Gilbert Stork
A Celebration of 35 Years in Research & Teaching

Thirty-five years spent in research and teaching is not a special milestone, but for friends of Gilbert Stork, it provides a welcome focus to think back on our happy associations with him as well as to look forward to the continued sharing in his creative life. One of Gilbert’s most remarkable qualities is his willingness to share time and energy with those who seek his counsel. His involvement could range from an in-depth discussion of the enamine reaction with a starting graduate student to whether a distinguished colleague should accept a position as president of a major academic institution or an industrial concern. In every situation, not only does he project complete attention, he gives it. At the end of a discussion with Gilbert, one certainly knows a lot more about chemistry and life, and, equally important, one’s self-confidence grows as a result of his generous encouragement and recognition. He always gives more than he receives. Although he is one of chemistry’s superstars, he is a warm human being.

It is no surprise that the graduate students and postdoctoral research fellows who have been associated with Gilbert are among the most productive and influential academic and industrial chemists in the world today. The deep loyalty felt by this group prompted the creation of an informal organization known as “The Stork Group.” In Gilbert’s Cope Award address in 1980, he presented, as his last slide, a list of the members of the Stork Group who presently hold positions in academia throughout the world. The slide listed over 110 names, an impressive number — indeed a possible world record for a single research professor. The names on the slide belong to distinguished chemists and Gilbert must feel proud of this remarkable list — a superb testimony to him.

Gilbert Stork’s birthday is celebrated by everyone throughout the world, for he was born on New Year’s Eve in 1921 in Brussels, Belgium. Shortly afterward, his parents, Jacques and Simone Weil Stork, moved to Paris where he spent his childhood.

Certain of Gilbert’s well recognized characteristics were evident in his youth. For example, his rigorous testing of reality began at an early age. One day his nurse took him to the park and carefully explained that he should under no circumstances go near a pond which was completely covered with water lilies. Since he found it difficult to believe that there could be any danger with what appeared to be a solid flower garden, he ran over to test the nurse’s story. When he was pulled out of the pool with his felt hat still firmly fastened under his chin, he believed her; but the poor nurse lost her job.

Gilbert’s qualities for leadership were evident quite early, for as a Boy Scout he was elected head of the choir in spite of being completely tone-deaf. This small group, under his command, was propelled to greater feats than music. With visions of Napoleon at Austerlitz, he conceived an adventure which would have taken his group into the woods of St. Cloud to emerge proudly from the wilderness by marching smartly down the main street in full view of the proud citizenry of Garches, a small suburb of Paris. Unfortunately, his leadership ran afoot with his lack of sense of direction and the group became completely lost in the woods. The adventure ended with a “Waterloo-like atmosphere” consisting of bedraggled Boy Scouts and hysterical parents.

His creative solutions to difficult problems also surfaced early. Gilbert’s favorite occupation during his summers at Ostend was going for pony rides on the beach. Unfortunately, he often had to wait fifteen to twenty minutes because of the long lines. One weekend, Gilbert was left in the care of his favorite Uncle Alex. Gilbert explained his problem to his uncle and proposed that the way to solve it was to have a pony of his own. His uncle found this to be a good solution, but when the pony appeared on the grounds of his home, considerable rumblings from the neighbors mounted to a volcanic eruption when Gilbert’s parents returned.

Gilbert’s interest in chemistry was sparked by an excellent teacher at the Lycée Janson de Sailly (other graduates we know are Jacques Barzun and Giscard d’Estaing). By the time his family came to the United States at the beginning of World War II, his course had been set. But Gilbert was in
a new country, did not speak English and was familiar only with the French educational system where, if one wished to attend a university, one simply showed up on the first day of classes. Consequently, there was a slight detour in his path toward the study of chemistry. He decided that the best way to select a university was to read everything published by the Office of Higher Education available in the New York Public Library. After two weeks of study, he concluded that the University of North Carolina was the best school for chemistry so he immediately boarded a bus for Chapel Hill. Unfortunately, the University did not expect him, was on a quarter system and furthermore, it was very cold in North Carolina at that time. After a brief and unsatisfactory interview, he got back on the bus, headed further south to St. Petersburg, Florida, still speaking no English and still not realizing that one had to apply for admission to a university. The details were sorted out eventually, and he was admitted to the University of Florida at Gainesville, in those days an all-male school with an enrollment of 3,000 students.

During the six weeks Gilbert had to wait for the semester to start, he enrolled in English and Speech courses in St. Petersburg. It was in those classes that he met Winifred Stewart whom he later married. Winifred has been his life's partner and they now have four grown children. It is difficult to imagine that Gilbert could be the person he is today, had he not married Winifred.

Problems of American procedures continued to plague Gilbert at Gainesville. For example, he thought it unnecessary to attend chemistry laboratory classes if he knew the answers to the questions in the laboratory notebook. Instead, he spent his time in the chemistry library where he read an extraordinary paper by Paul Rabe published in the 1930's on the synthesis of dihydroquinine. Quinine had become an important national problem, and after reading Rabe's paper, Gilbert devised a synthesis of quinine. On the basis of this synthesis, he was given his own laboratory. The grumble on his non-attendance of laboratory courses lowered considerably. The starting material for his synthesis was bis(2-chloroethyl)methyamine which he prepared in large quantities. During the preparation, his left hand became a red, swollen glob with fingers no longer visible. Some time later, it was learned that this compound was a lethal nerve gas - we are lucky to have Gilbert to write about today. He graduated in two-and-a-half years from the University of Florida, in part, because of the many credits he received for having taken Greek in France, and obviously, because he was a rather special student.

His chemical interests had been aroused by pyridine and piperidine compounds, so Gilbert decided to do graduate work with either Professor Roger Adams at the University of Illinois or Professor S.L. McElvain at Wisconsin. Again, he boarded a bus, this time for Urbana, Illinois, but he was told that Professor Adams could not see him that day. Gilbert therefore continued his bus trip to Madison, Wisconsin. He saw Professor McElvain and gave him his projected synthesis of quinine to think about overnight. Professor McElvain was so impressed with the synthesis that Gilbert started working in the laboratory the following day. This work on cis-3,4-disubstituted piperidines inspired his life-long interest in the stereochemical control of reactions. In 1946 he devised a synthesis of 6-methoxy-α-tetralone, which he probably wishes he had patented, for it is still the method used to make starting material for aromatic steroids such as estrone.

On the exam and, instead of being praised, Gilbert was accused of giving his students the answers to the questions on the examination. The coup de grace came, however, when some of his students climbed out a laboratory window to beat the lunch crowd at the student union. This heinous crime was discovered by the major domo of the laboratory and Gilbert was asked to give the students' names. He refused in the name of honor. The fact is that he had not remembered their names and did not know who had skipped out. As a result of this incident, he was summarily fired as a teaching assistant and was told that he was an incompetent teacher and should plan on doing something else with his life. The dark cloud had a silver lining, for the next day he received a university fellowship which permitted him to devote full time to research.

Two of his closest life-long friendships developed while he was at Wisconsin. Carl Djerassi was a fellow graduate student and William S. Johnson was a member of the staff. Gilbert's friendship with Carl was cemented by such episodes as sharing living quarters in Mexico City for three days during a complete shut-off of the city's water supply.

After receiving his degree from Wisconsin, he joined Lakeside Laboratories in Milwaukee as the only senior research chemist in the company. By day he worked as a medicinal chemist; by night he worked on his own ideas.

Bill Johnson was responsible for encouraging Gilbert to apply for an independent fellowship at Harvard. Part of the application was an original research proposal.

The Three Musketeers.
on the synthesis of estrone. Professor Paul Bartlett, then Chairman of the Department, called and offered him an instructor-ship at Harvard. Gilbert promptly accepted.

Harvard was an incredibly exciting and fun place to be when Gilbert was there. Many still remember the colloquia he presented during those years, especially one on the stereochemistry of polyene cyclization in which he proposed what is now known as the “Sterk-Eschenmoser Hypothesis.” Notable achievements during the Harvard years include the total synthesis of cantharidin, a significant accomplishment since no entirely stereospecific synthesis of a natural product had yet been reported. The synthesis was completed at 4:00 a.m. on July 4, 1951 while Albert Burgstahler, the graduate student working on the problem, alternated between working up the last step and singing Gregorian chants on the roof of the

The inner sanctum at Columbia, 1953.

ly not to break the glass contents, the thick white line painted across the sixth-floor corridor which was meant to keep organic chemists from crossing into Professor Victor K. La Mer’s territory, and Gilbert’s office, which would have made a rather spacious closet. This closet had had a distinguished history since it had served as the office of Professor Arthur C. Cope and Professor William E. von Doering.

A distinguished event occurred there when Linus Pauling came to discuss the possibility of Gilbert’s moving to Cal Tech. At that time, the Columbia Chemistry Department had a regular table at the Faculty Club and Gilbert remembers, with mischievous pleasure, that he took Pauling to lunch making certain that he and Pauling could be seen from the Chemistry table. The physical chemists, not knowing of the Cal Tech offer, could not understand why the great physical chemist, Pauling, would choose to discuss scientific matters with Gilbert rather than with them.

Gilbert has had a distinct elegance and style in all his endeavors — from playing table tennis to working in the laboratory where he resembles a Grand Prix racing driver. An example is the synthesis of bicyclo[4.1.0]heptanone from $m$-hydroxybenzoic acid. It was calculated to take eight steps and Gilbert asserted that it would

A novel aspect of chemistry.

chemistry building. The determination of the structure of cedrene was also completed during the Harvard period. At the same time, Carl Djerassi arranged for Gilbert to be a consultant at Syntex. His contribution to the introduction of an 11-oxygen function into sterols unsubstituted in ring C led not only to an important industrial method, but also to Gilbert’s and Carl’s appearance in a Life magazine photograph.

At the urging of Professor Louis Hammett, Gilbert joined the Department of Chemistry of Columbia University in 1953 as an Associate Professor. Columbia was a far cry from what it is today, both physically and academically. I remember the alchemical nature of the laboratories, heightened by the dimness of the light, the effort it took to pull open the cast-iron laboratory drawers while trying desperate-

How many of these “distinguished looking” chemists can you identify? See page 10.
take only two days to prepare. The rest of us roared with laughter at this unrealistic suggestion and the substantial bet of $100 was made that he could not do it in two days. The race began on Saturday morning and by 7:00 on Sunday evening, the compound was ready to be sent for analysis. I will always remember paying off part of the bet.

There is one aspect of Gilbert’s life that has bewailed me. How can such an intelligent man insist on buying cars which, without fail, are incapacitated at least fifty percent of the time? One of these ‘treasures’ was a sporty, white Simca with red leather seats. After spending a good amount of money transporting it from France, a small fortune to adapt it to New Jersey requirements and further fortunes to keep it running, the engine blew up as he was driving to Yale to present the Treat B. Johnson lectures. With the usual Storkian luck, the car was on an incline which terminated in front of a gas station. Gilbert arranged for the car to be fixed and took a train to New Haven. He retrieved the car on the way back after contributing Yale’s honorarium to the garage mechanic. While on the Merritt Parkway, the engine exploded again. This was the end of Gilbert’s endurance and he decided to abandon the car then and there. While he was removing the license plates, a state trooper stopped to check on the strange situation. With characteristic aplomb, Gilbert struck a bargain — the state trooper could have the car in exchange for a ride to the nearest railway station. I have often wondered who made out best on that one.

Then, there was the elegant, British-racing-green Jaguar with its impeccable styling. It was nursed through frequent nervous breakdowns by a mechanic complete with French beret and eyes which projected megabucks. The demise of this thoroughly bred was spectacular. One wet evening Gilbert was crossing the George Washington Bridge when the car lurched to a stop. Concurrently, a series of collisions occurred on the opposite side of the bridge. The bridge patrol was baffled by the number of simultaneous accidents until a wheel was spotted careening back and forth, between and over the cars like a volley ball. This was Gilbert’s wheel which eventually plunged into the Hudson River. Shaken by these six accidents, Gilbert and the Jaguar parted company the next day.

At present, his “true love” is a 1957, silver, two-seater Thunderbird. What marvelous shape! But don’t step too firmly on the floorboards or your feet will hit the pavement.

Stork has been the master architect of Columbia’s organic group. The emergence of this faculty from relative obscurity in 1952 to its present position of eminence would not have taken place without his remarkable intuition and judgment. Because of his ability to recognize young people of outstanding talent and to persuade them to join Columbia, the building of the organic group was accomplished (with one exception) with appointments at the non-tenure level. Perhaps one of the most striking attributes of the Columbia organic faculty is its ability to combine a passionate involvement in chemistry with a relaxed and friendly attitude. Gilbert has had much to do with this feeling which extends to the graduate students of all the organic research groups.

The core of Gilbert Stork’s life has been his creative research in organic chemistry. Since I do not have the expertise to give a summary of his glittering scientific achievements, I wish to express my thanks to those who have contributed the material for this section.

Stork’s achievements fall into three “naturally occurring” areas: the total synthesis of complex natural products; the creation of new synthetic methods; and, finally, the investigation of reaction mech-
anisms. To separate synthesis from the creation of new reactions is totally arbitrary because of the strong interplay between these two areas. It has been Stork’s philosophy that the purpose of a total synthesis must be more than a demonstration of the brilliance of the molecular architect in the clever orchestration of known synthetic methods. In his search for new reactions he has concentrated his efforts in seeking new and controlled methods of forming carbon-carbon bonds, the foundation of organic synthesis.

A. TOTAL SYNTHESIS

From the very first, Stork’s syntheses were designed to be stereospecific. The importance of achieving a stereoselective synthesis had not been considered or recognized before Stork. This principle, now universally appreciated and used, was already a factor in his design of the synthesis of cincholoison (1946), a cis-3,4-disubstituted piperidine related to hydroquinine; and in the totally stereospecific synthesis of cantharidin in 1951. It is of historical interest, with respect to the development of stereocontrolled syntheses, that his very first paper (1945), a communication of which he is sole author, reported the synthesis of a 3,4-diaminofuran, the starting material for a planned stereospecific synthesis of biotin. The correct stereochemistry was to follow from catalytic hydrogenation of a 2,3,4-trisubstituted furan followed by further stereo-controlled transformation of oxabiotin to biotin itself.

Many of these total syntheses served as the focus for the development of new reactions. The stereospecific synthesis of the pentacyclic triterpene lupeol is a showcase of the power of the regiospecific formation and trapping of enolates. In this molecule a system of ten asymmetric centers was put in place with complete stereochemical control. Regiospecific formation and trapping of enolates was also used to simplify markedly the building of such diverse molecules as the prostaglandins, lycopodine and some of the steroids.

It would be surprising if enamines had not found an important use in a variety of these total syntheses: it will suffice to mention the construction of yohimbine and aspidospermine. Even seemingly small synthetic contributions have had considerable impact: the synthesis of 6-methoxy-α-tetralone, the previously mentioned starting material for the aromatic steroids, was based on Stork’s discovery that the catalytic hydrogenation of substituted naphthalenes could be made to take place in the unsubstituted ring.
B. SELECTED SYNTHETIC METHODS

It is the creation of new synthetic methods rather than the area of total synthesis which Stork believes will be his most valuable contribution to organic chemistry. These methods can be divided conveniently into three parts.

The first, and perhaps foremost, concerns the regioselective formation of carbon-carbon bonds alpha to a carbonyl group. To understand what impact this has had on modern chemistry, it must be recalled that, prior to this work, it was impossible to achieve such a fundamental operation as the alkylation of an aldehyde with an alkyl halide or with an electrophilic olefin, or the regiospecific (the word did not even exist) formation of a carbon-carbon bond on one or the other side of a ketone carbonyl. Gilbert Stork created many important synthetic transformations which contributed greatly to the explosive development of organic synthesis. His creative brilliance can be judged by the following work:


2) Demonstration that lithium enolates can be alkylated and carbonated without loss of any built-in regiospecificity (1961; 1965).

3) First and most widely used method for the specific formation of a lithium anion on either side of a ketone carbonyl (1961; 1965).

4) Generation of specific lithium enolates by cleavage of silyl enol ethers with lithium alkyls (1968).

5) Extension of the regiospecific lithium enolate alkylation reaction to aldol condensations (1974), and to the first general solution to the problem of trapping these enolates with Michael acceptors (via α-silylated vinyl ketones, esters ... ) (1973, 1974).

6) Extension of the regiocontrolled enolate processes to cyclopropyl ketones (1971) and to enediones (1980).

7) First demonstration that imines can be deprotonated to imine anions (“metalloenamines”) thus leading to a general method for the monoalkylation of ketones (saturated and conjugated) and aldehydes with a wide variety of halides (1963).

8) First extension of the process to \( N,N \)-dimethylhydrazones (1971). Further extension to regiospecific arylation via the \( N,N \)-dimethylhydrazones of epoxyketones (1978). These processes have seen numerous applications by many groups in recent years,
especially in the area of asymmetric induction using chiral imines and related substances.

A variety of novel systems have been designed which allow the storage of reactive carbonyl systems in relatively stable forms until needed (cf. 9-13):

9) The isoxazole annelation, as illustrated in a total synthesis of progesterone (1967).

10) Another form of isoxazole annelation as exemplified by the construction of the most characteristic ring of the tetracyclines (1979).

11) Introduction of the vinylsilane moiety as an enol (i.e., latent ketone or aldehyde) precursor (1971).

12) Protected cyanohydrins (1971, 1974, 1975) as acyl carbanion equivalents in the formation of cyclic and acyclic ketones.


15) Reductive cyclization of unsaturated (e.g., acetylenic) ketones (1965).

16) Formation of various-size rings by intramolecular opening of epoxynitriles. This leads, inter alia, to one of the few non-photochemical syntheses of functionally substituted cyclobutanes (1974).


18) General synthesis of 1,4- and 1,5-diketones by carbonyl-assisted hydration of acetylens (1964).

19) Direct C-21 hydroxylation in the construction of the dihydroxyacetone side chain of corticoids (1957).

20) Stereocontrol in vicinally substituted rings and trans hydrindanes by internal Michael addition (1982).
21) Functionally substituted rings via the cyclization of olefinic vinyl radicals (1982).

\[
\begin{align*}
\text{R} & \quad \text{C} \quad \text{O} \\
\text{C} \quad \text{C} \quad \text{R} & \quad \text{N} \\
\text{O} \quad \text{C} \quad \text{Ar} & \quad \text{H} \\
\end{align*}
\]

\[
\begin{align*}
\text{H} & \quad \text{C} \\
\text{O} \quad \text{Ar} & \quad \text{H} \\
\text{H} \quad \text{C} \quad \text{Ar} & \quad \text{CH}_3 \\
\end{align*}
\]

C. MECHANISTIC AND STEREOCHEMICAL STUDIES

These studies were conducted not so much for their own sake as for their potential in leading to controlled synthetic processes.

1) Investigation of the stereochemistry of the \(S_{N}2\) reaction (1956, 1977).

\[
\begin{align*}
\text{O} \quad \text{C} \quad \text{Ar} & \quad \text{R} \\
\text{R} & \quad \text{N} \\
\text{H} & \quad \text{C} \quad \text{Ar} \\
\text{H} & \quad \text{C} \\
\end{align*}
\]

2) Stereochemistry of the Favorskii rearrangement of \(\alpha\)-haloketones (1960).

\[
\begin{align*}
\text{X} \quad \text{C} \quad \text{O} \\
\text{R} & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{O} \quad \text{C} \quad \text{Ar} \\
\end{align*}
\]

3) The mechanism of the racemization of usnic acid. This problem had long baffled the chemical community and was explained as a reversible electrocyclic reaction (1955).

\[
\begin{align*}
\text{CO}_2 \quad \text{H} \\
\text{CH}_3 & \quad \text{H} \\
\text{H} & \quad \text{CO} \quad \text{H} \\
\end{align*}
\]


\[
\begin{align*}
\text{C} \quad \text{H}_2 \quad \text{O} \quad \text{Ts} \\
\text{R} & \quad \text{O} \quad \text{C} \quad \text{Ts} \\
\text{O} \quad \text{H} \quad \text{C} \quad \text{O} \\
\end{align*}
\]

5) We end by referring to the Stork-Eschénmoser hypothesis. The conclusion that the stereochemistry of a bicyclic cation made by a concerted reaction from an acyclic triene must be a \(\text{trans}\) bicyclic system was advanced in 1950. The possibility was then raised that this theoretical conclusion might well be the explanation of the \(\text{trans-anti-trans}\) arrangement so prevalent in polyterpenes and steroids. This has been amply confirmed, biogenetically as well as by the superb synthetic work of W. S. Johnson.

\[
\begin{align*}
\text{R} & \quad \text{H} \\
\text{R} & \quad \text{H} \\
\text{H} & \quad \text{CH}_3 \\
\end{align*}
\]

Not many people have had greater impact on modern organic chemistry than Gilbert Stork. He certainly has left his imprint on those who have had the good fortune to be associated with him.

HONORS AND AWARDS

Award in Pure Chemistry of the American Chemical Society (1957)
Baekeland Medal (1961)
D.Sc. (Hon.) Lawrence University (1961)
Elected to the National Academy of Sciences (1961)
Elected to the American Academy of Arts and Sciences (1962)
Harrison Howe Award (1962)
Edward Curtis Franklin Memorial Award, Stanford University (1966)

American Chemical Society Award for Creative Work in Synthetic Organic Chemistry (1967)
SOCMA Gold Medal (1973)
Roussel Prize, Paris (1978)
D.Sc., Honoris Causa, Université Pierre et Marie Curie of Paris, (1979)
Nichols Medal (1980)
Arthur C. Cope Award (1980)
Edgar Fahs Smith Award (1982)
Willard Gibbs Medal (1982)
National Academy of Sciences Award in Chemical Sciences (1982)


About the Author

Frances Hoffman has been a friend of Gilbert Stork for over thirty years.

After graduating from Mount Holyoke College, she obtained a position with Carl Djerassi at Ciba. When he left to join Syntex in Mexico, she went to work with Gilbert in the Department of Chemistry at Harvard and in 1953 moved to Columbia's Department of Chemistry with the Stork group.

From 1954 to 1961 she was a member of Lewis H. Sarett's research department at Merck and Company where she did research in the field of steroid chemistry.

In 1961 she returned to the Department of Chemistry of Columbia University as Director of Chemical Laboratories. For the past twenty years she has contributed to the growth and development of that department. At present, she is deeply involved in the development of plans for a new chemistry building.
Recent Applications of Homogeneous Catalysis to Organic Synthesis

INTRODUCTION

Transition metal-assisted organic synthesis has enjoyed explosive growth and exploitation in the past decade. One of the most exciting advances is the adaptation of stoichiometric homogeneous reactions to catalytic reactions, largely decreasing the amount of noble metal needed.

Nearly everyone is familiar with heterogeneous catalysis, usually as applied to hydrogenations. Actually, these catalysts can be used in the synthetic applications to be discussed, but are extremely inefficient compared to their solubilized counterparts. Homogeneous catalysis embodies several important advantages:

1) Each expensive metal atom is an "active site", as opposed to just those on a surface.
2) Each atom is in an identical environment, increasing reaction specificity.
3) Selectivity can be "fined-tuned" by the judicious choice of ligands, solvents, and other variables.

4) Heat is more efficiently dissipated, and reaction conditions are generally milder.
5) Mechanistic studies are easier, allowing better understanding and thus greater control of reactions.

The sheer vastness of this expanding field precludes in-depth treatment of any particular aspect in this survey. The aim is, rather, to provide the reader with an overview of the very diverse, useful, and intriguing reactions made possible by homogeneous catalysis. Specifically omitted are hydrogenation reactions and those employing chiral ligands.

MECHANISTIC CONSIDERATIONS

Transition metals undergo reaction pathways impossible for organic molecules, thus, complexation of a functional group to a metal usually drastically alters its normal chemistry. In order to aid in the planning and execution of a catalytic reaction, a short summary of pertinent organometallic reactions will be presented. In this review, the term "metal" (M) will always refer to a Group VIII metal.

Both σ- and π-organometallic complexes are involved in catalysis. σ-Complexes usually arise from the oxidative addition of a metal to an organic halide. Since the metal loses two electrons in the process, ligands which increase electron density facilitate the reaction while electron-withdrawing ligands impede it. Thus, phosphines (strong σ-donors) aid oxidative addition while carbonyls (strong π-acceptors) retard it.

σ-Complexes (e.g., 1) undergo five major reactions, summarized in Scheme I. Reductive elimination is the reverse of oxidative addition, and often constitutes the last step of a catalytic reaction. Insertion of carbon monoxide affords a metallated acyl species (2), while alkenes insert to give complexes such as 3. If a β-hydrogen is present, (syn) β-elimination of metal hydride yields an alkene, 4 (of course, this can also...
occur in 1 if R contains a β-hydrogen). Finally, transmetallation with another organometallic species affords σ-complex 5.

Electrophilic attack by metal on an alkene can result in the formation of either a π-olefin (6) or a π-allyl (7) complex. The most important consequence of such interaction is activation of the involved carbon atoms toward nucleophilic attack.

**LIGAND ABBREVIATIONS**

A great many ligands are employed in transition-metal chemistry. Throughout this survey standard abbreviations are employed: acac = acetylacetonate; DIPPHOS = 1,2-bis(diphenylphosphino)ethane; dba = dibenzylideneacetone; COD = 1,5-cyclooctadiene; NBD = norbornadiene; dpff = 1,1'-bis(diphenylphosphino)ferrocene.

**ALLYLIC ALKYLATION**

The nucleophilic alkylation of allylic systems constitutes one of the most thoroughly studied aspects of transition-metal-catalyzed reactions. Basically, a metal (usually Pd) induces ionization of an allylic unit (often an acetate) which is then attacked by a nucleophile. Studies on the racemization of optically active allylic lactones implicate a symmetrical π-allylpalladium intermediate (e.g., 8), although recent evidence indicates that other species may be involved.

Many nucleophiles participate in this reaction. The regiochemical outcome is highly dependent upon the nature of the nucleophile, the allylic substituents, and the ligands on the metal.

1,3-Diketones are favorite alkylation agents, although alkyl α-sulfonylacettes are often more synthetically useful due to the variety of possible further manipulations. The nucleophile can be used directly (eqs. 1, 2) or is sometimes first deprotonated (eqs. 3, 4). Since the leaving group departs and the nucleophile enters trans to the metal, retention of configuration is observed (eq. 3). Scheme II outlines a short synthesis of phoracantholide J, in which the penultimate step involves an intramolecular alkylation. (±)-Reefeiolide has also been prepared via this approach.

Other nucleophiles recently applied to this reaction include enamines (eq. 5), alcohols (eq. 6), and amines (eq. 7). The latter
are particularly useful intramolecularly (eq. 8) and have enabled the facile construction of N-heterocycles (e.g., isouquinuclidine). 28

Organometallic species also serve well; compounds of magnesium (eq. 9), tin (eq. 10, or tin enolates), 21 zirconium, 24 aluminum, 21 and others have been employed successfully.

**ALLYLIC TRANSPOSITIONS**

**REARRANGEMENTS**

In the absence of added nucleophiles, allylic acetates can undergo 1,3-transposition, usually toward the less hindered allylic terminus. The E isomer generally predominates (eqs. 11 and 12). Since the acetate departs and enters *trans* to palladium (as noted previously), efficient transfer of chirality is possible (eq. 13).

A general furan synthesis involves rearrangement of an acetylated cyanohydrin followed by ester saponification, nitrile reduction, and acid-catalyzed cyclization (eq. 14).

Various Pd species also catalyze sigmatropic rearrangements, usually of the [3,3] variety involving heteratoms. Of particular note is the propensity for S→N migration (eqs. 15 and 16). A potentially very useful reaction employs a Pd(OAc) 2-catalyzed allyl vinyl ether shift to construct prostaglandin precursors (eq. 17).

**ISOMERIZATIONS**

Although valence isomerizations have been observed (e.g., eq. 18), positional isomerization of alkenes is most often the purpose of metal catalysis. Usually the thermodynamically more stable isomer is produced, as noted in a new synthesis of hydroquinones (eq. 19).

A useful facet of ruthenium catalysis is the tendency for isomerization of allyl to vinyl ethers, allowing the preparation of enol ethers from allylic alcohols (eq. 20). A short, general tetrahydrofurancarboxaldehyde synthesis exploits this phenomenon (Scheme III). 11

Enol ethers also result from rearrangement of alkoxyxyclopropanes (eq. 21).

**OLEFIN DIMERIZATIONS**

**ADDITIONS**

Metal-catalyzed oligomerization of butadienes has been known for many years. 17 Often, dimerization of the olefin is followed by attack of a nucleophile, resulting in the net attachment of a 2,7-octadiene fragment (eq. 22). Additionally, methylencyclopropane codimerizes with CO, or certain olefins to afford some interesting products; Pd(dbq) 2 is used for these transformations (Scheme IV).
Olefins also undergo electrophilic addition of halogenated compounds, as seen in a novel, one-step γ-lactone synthesis (eq. 23). If the olefin possesses two allylic hydrogens, elimination to form 4-alkyldienbut-2-enolides is possible (eq. 24). The reaction also works well with silyl carboxylates.

Trimethylenemethane, a Diels-Alder diene equivalent, can be generated in situ to react with a variety of dienophiles in a unique three-carbon annulation technique (eq. 25).

**Cyclizations**

Many 1,5- and 1,6-diienes are cyclized in the presence of palladium. Although ring size can be governed by the oxidation state of the catalyst (eq. 26), five-membered rings usually are formed. Functionalized cyclopentenes and γ-methylenebutyrolactones have been constructed in this way.

Miscellaneous cyclizations which have appeared recently include the formation of N-heterocycles from α,ω-diamines (related to the disproportionation of primary amines), and the one-step synthesis of quinolines and chromans from monocyclic precursors.

**The Heck Reaction**

One of the most general and useful applications of homogeneous catalysis is the Heck reaction, in which organic halides are coupled with olefins under palladium catalysis (eq. 27). The reaction is remarkably selective, and almost any functional group can be present in either reactant. Generally, the halide prefers the less-substituted carbon of the olefin, whose stereochemistry is retained consistent with the syn addition of an RPdX species followed by syn β-elimination of palladium hydride. Typically, Pd(OAc)₂ is used in conjunction with tri-o-tolylphosphine; triethylamine is added to scavenge the HX produced. Scheme V outlines some representative examples with aromatic bromides. Note that allylic alcohols (or their trimethylsilyl ethers) afford carbonyls; these arise from vinlylic alcohols created in the elimination step. A recent synthesis of curcumone makes use of this transformation.

Aryl iodide-palladium complexes require no phosphines for stabilization; thus, selective reactions (e.g., eq. 28) are possible. o-Iodoanilines are cyclized with dimethyl maleate to 2-quinolines in one step. The aryl component can also be organometallics (e.g., boron and mercury) or a diazonium salt. Very recently, N-substituted anilines have been shown to be equally effective, affording β-aminooenones.
Vinyl halides also couple smoothly, exhibiting the same high stereoselectivity and generality, as indicated in eqs. 29 and 30.

**CONJUGATE ADDITIONS**

Many 1,4-additions are expedited by metal catalysis. The nucleophilic species is usually organometallic, although amines can often be effective.** Arylmercurials are commonly employed (eq. 31), although tin and many other metal halides also add; the choice is mainly one of synthetic convenience.

Alkenylzirconiums, easily prepared from alkynes, smoothly add to both enones and dienes (eq. 32) under Ni(0) catalysis; prostaglandin precursors have been prepared via this route.** Alkynylalanes also pose no problem (eq. 33).

**COUPLING REACTIONS**

A species such as 5 (Scheme I), formed via transmetallation, often undergoes reductive elimination to complete a very useful coupling reaction. A host of metals and halides can participate; as before, their choice is usually one of synthetic expediency. Thus, magnesium** (eq. 34) and boron** (eq. 35) compounds are commonly used, although tin, silicon, zirconium, zinc, aluminum, lithium, and others are effective. The halides involved include aromatic, alkyl, benzyl, propargyl, and allenyl derivatives. The major asset of this method is the retention of olefin geometry resulting in products of exceptional isomeric purity.

Acyl halides can couple with organometallics to afford ketones in high yield. Benzoyl chloride has been coupled with vinyl, trimethylsilyl, benzyl, aryl, and alkyl groups.

Aryl and vinyl halides couple with acetylenes in the presence of Pd(II) and Cu(I) (eq. 36); even sensitive iodouracils are compatible.**

A related reaction allows the displacement of enol ethers by Grignard reagents to afford alkenes (eqs. 37 and 38). Interestingly, enol phosphates are displaced preferentially to enol thioethers.**

**CARBONYLATION**

Metallated carbonyls (e.g., 2, Scheme I) which arise from CO insertion react with an array of nucleophiles to afford ketones. Scheme VI illustrates the diversity of this reaction. Intramolecular transformations include the synthesis of lactones from o-iodobenzyl alcohols, indoles from o-allyl amines, and berbinos from papaverines.**

When carboxylated in the presence of carboxylates, aryldiazonium species afford mixed anhydrides which thermally...
rearrange into symmetrical aryl anhydrides (eq. 39).

Alkenylboranes readily carboxylate in methanol to give α,β-unsaturated esters.\(^\text{163}\) In the absence of added nucleophiles, alkenylmercury compounds dimerize onto CO to produce divinyl ketones (eq. 40), previously very difficult to prepare. Intramolecular alkeno carboxylations have enabled the one-step construction of substituted 2(SH)-furanones\(^\text{114}\) and α-methylene-γ-lactones.\(^\text{109}\)

Small-ring heterocycles also insert CO, as in the preparation of α-phenylpropiolactone from styrene oxide\(^\text{106}\) or of fused β-lactams from aziridines (eq. 41). The latter process would appear to have great potential for antibiotic synthesis.

In the presence of allyl or benzylic chlorides and a palladium catalyst, cyclo ethers open to form α-chloro ethers (eq. 42).

**DECARBOXYLATION**

In the presence of base, allylic acetates can be oxidatively eliminated to afford olefins. The reaction is most facile when an aromatic (e.g., eq. 43) or conjugated system results; the latter was exploited in a recent homoazulene synthesis.\(^\text{110}\) α-Carboxylic acids depart as easily as protons (e.g., eq. 44); a vitamin A precursor was constructed in this manner.\(^\text{112}\)

Allyl esters decarboxylate in a new carbon-carbon bond-forming reaction (eq. 45) which also allows the preparation of ethers from carbonates.\(^\text{114}\)

**OXIDATIONS**

Transition-metal catalysis enables mild, selective oxidations under neutral or basic conditions. Under Ru catalysis, alcohols are oxidized to either aldehydes or acids depending on the oxidant [PhIO vs. PhH(OAc)\(_2\)].\(^\text{113}\) Other oxidants include CCl\(_4\), \(^\text{116}\) aryl bromides, and oxygen (specific for allylic alcohols, eq. 46). Such methods offer an attractive alternative to the acidic chromium systems.

Terminal olefins are oxidized to methyl ketones under Pd(II) catalysis in an extension of the industrially important Wacker process.\(^\text{116}\) The transformation involves a formal addition of H\(_2\)O; the added oxidant (even air!\(^\text{119}\) serves to re-oxidize extruded Pd(0). Eq. 47 illustrates a two-step cyclopentenone synthesis based on this conversion, which has recently been shown to apply to enone systems (eq. 48).

**REDUCTIONS**

Metals catalyze many useful reductions besides hydrogenations. In the presence of Ru complexes, ketones are reduced to alcohols in high yield by formic acid\(^\text{113}\) or...
trialkoxylsines. 124 Interestingly, the former effects the 1,4-reduction of chalcone to yield the saturated ketone. 125

Aryl ketones are smoothly reduced to methylenes by a NaBH₄/PdCl₂ system in a mild, neutral alternative to Wolff-Kishner or Clemmensen chemistry. 126 Imines are easily reduced to amines by isopropanol under rhodium catalysis. 127 Finally, Li(r-Bu₂O)₂AlH can be replaced by n-Bu₂SnH/Pd(0) for the preparation of aldehydes from acid chlorides. 128

**DIAZO CHEMISTRY**

α-Diazoketones are valuable precursors to reactive carbonyl species. 129 Classically effected by copper, the decomposition of α-diazoketones proceeds in high yield in the presence of Rh(II) carboxylates (commonly acetate). Cycloheptatrienes can be prepared from substituted benzenes in high chemical and stereochemical yield using alkyl diazoacetates (eq. 49).

Z-α,β-Unsaturated esters result from treating α-diazoesters with Rh(OAc)₃ (eq. 50). The key step in an elegant synthesis of α-damascone involved the conversion shown in eq. 51; this mild oxidation avoids the partial retro-aldol reaction which always accompanies the acid treatment of α-diazo-β-hydroxy ketones. 130

A recently developed intramolecular carbene addition allows easy entry into the 1-carbapenam ring system from diazo precursors (eq. 52). Yields are high, and rarely is more than one isomer produced. The generality of this method is indicated by its recent application in the syntheses of Antibiotic PS-5 131 and epithemamin. 132

**CONCLUSION**

Space limitations have prohibited the coverage of many useful miscellaneous reactions mediated by homogeneous catalysis, among them N₁₄₆ and C-alkylations, 137 epoxide openings, 138 desulfurizations, 139 and Wittig-type olefinations. 140 It is hoped, however, that this short survey has instilled in the reader an appreciation of homogeneous catalysis as a rich and diverse methodology not to be neglected in planning a synthetic strategy. Many of the transformations covered in this review simply have no one-step synthetic alternative. Hopefully, broader awareness of this exciting field and its tremendous potential will result in greater application in organic synthesis.

**References**

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